Comprehensive medical reference and review for the
Medical Council of Canada Qualifying Exam Part I and the
United States Medical Licensing Exam Step 2

32nd Edition

Editors-in-Chief:
Zamir Merali and Jason D. Woodfine

Wherever the art of medicine is loved,
there is also a love of humanity.

– Hippocrates

Toronto Notes for Medical Students, Inc.
Toronto, Ontario, Canada
+ Thirty-second Edition

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The editors of this edition have taken every effort to ensure that the information contained herein is accurate and conforms to the standards accepted at the time of publication. However, due to the constantly changing nature of the medical sciences and the possibility of human error, the reader is encouraged to exercise individual clinical judgement and consult with other sources of information that may become available with continuing research. The authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this textbook, atlas, or software and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. In particular, the reader is advised to check the manufacturer’s insert of all pharmacologic products before administration.

FEEDBACK AND ERRATA
We are constantly trying to improve the Toronto Notes and welcome your feedback. If you have found an error in this edition please do not hesitate to contact us. As well, we look forward to receiving any comments regarding any component of the Toronto Notes package and website.

Please send your feedback to: feedback@torontonotes.ca

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past and present contributors
and
supporters of Toronto Notes
who have made the production of the 2016 edition possible!

The Toronto Notes is dedicated to helping fund many charitable endeavours and medical student initiatives at the University of Toronto's Faculty of Medicine. Programs that have received Toronto Notes funding include:

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- Nishant Fozdar Memorial Award
- Graduating Medical Class Scholarships and Bursaries

**Note:**
Many of you have wondered about the Toronto Notes logo, which is based on the rod of Asclepius, the Greek god of medicine. The rod of Asclepius consists of a single serpent entwined around a staff. This icon symbolizes both rebirth, by way of a snake shedding its skin, and also authority, by way of the staff.

In ancient Greek mythology, Asclepius was the son of Apollo and a skilled practitioner of medicine who learned the medical arts from the centaur Chiron. Asclepius’ healing abilities were so great that he was said to be able to bring back people from the dead. These powers displeased the gods, who punished Asclepius by placing him in the sky as the constellation Orphiuchus.

The rod of Asclepius is at times confused with the caduceus, or wand, of Hermes, a staff entwined with two serpents and often depicted with wings. The caduceus is often used as a symbol of medicine or medical professionals, but there is little historical basis for this symbolism.

As you may have guessed, our logo uses the rod of Asclepius that is modified to also resemble the CN Tower – our way of recognizing the university and community in which we have been privileged to learn the art and science of medicine.

Thomas O’Brien, MD
Class of 2009
M.D. Program, University of Toronto
Dear Readers,

As the Editors-in-Chief of Toronto Notes 2016 we are proud to present this updated edition.

Toronto Notes began humbly in 1985 from a set of student notes circulated among medical students at the University of Toronto. Over time, Toronto Notes has grown into one of the premier study resources for generations of Canadian medical school graduates. This rich history has led to our firm commitment to publish a comprehensive study resource for medical students engaged in clinical rotations and studying for both the USMLE Step 2 and Canadian MCCQE Part 1.

For over 30 years we have remained committed to our original vision. The 2016 edition of Toronto Notes contains significant improvements including:

1. A new emphasis on ‘Approaches to Common Clinical Presentations’ in addition to traditional content organized by disease.
2. A completely revised Psychiatry chapter incorporating the DSM-V in a quick-to-reference and readable format.
3. The Toronto Notes Quiz App, which is available for free on iTunes and Google Play. This app contains hundreds of questions allowing users to test themselves on the content contained within Toronto Notes.
4. A significantly improved interactive eBook with many new high-quality colour images.
5. A brand-new Clinical Handbook that is more concise, has numerous new figures, and features approaches to hundreds of common clinical situations.

Toronto Notes 2016 is produced by Toronto Notes for Medical Students Inc., which is a non-for-profit organization supporting various charity organizations in the city of Toronto. This year Toronto Notes for Medical Students has supported organizations including medical school clubs, community outreach groups, student bursaries and scholarships, and the Canadian Cancer Society. Your purchase of Toronto Notes 2016 is much appreciated by these well-deserving groups.

We would like to highlight the exceptional work of our team, composed of over 150 medical students, medical illustrators/artists, and faculty members at the University of Toronto Faculty of Medicine. Without the tireless effort expended by these individuals the production of Toronto Notes 2016 would not have been possible. In particular, we would like to highlight the work of the executive team, all of whom made personal sacrifices in balancing clinical work with the responsibilities asked of them. We also want to highlight the work of Jesse Lu and Kota Talla, without whom the production of the Toronto Notes Quiz App would not have been possible. Lastly, we would like to thank our partners at Type & Graphics Inc., particularly Enrica Aguilera, for their guidance during the production of Toronto Notes 2016.

We hope you find Toronto Notes 2016 enhances your medical knowledge and allows you to perform better on both your clinical rotations and licencing exams. We continue to encourage feedback – this year, we have read and incorporated every piece of feedback we received about the previous edition of Toronto Notes. On behalf of the Toronto Notes 2016 team, we wish you success in your studies.

Sincerely,

Zamir Merali, BSc. and Jason D. Woodfine, BSc.
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We would like to acknowledge the exceptional work of all previous Toronto Notes (formerly MCCQE Notes) Editors-in-Chief and their editorial teams. The 32nd edition of this text was made possible with their contributions.

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This book has been designed to remain as one book or to be taken apart into smaller booklets. Identify the beginning and end of a particular section, then carefully bend the pages along the perforated line next to the spine of the book. Then tear the pages out along the perforation.

The layout of Toronto Notes allows easy identification of important information. These items are indicated by icons interspersed throughout the text:

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<th>Icon Name</th>
<th>Significance</th>
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<td>Key Objectives</td>
<td>This icon is found next to headings in the text. It identifies key objectives and conditions as determined by the Medical Council of Canada or the National Board of Medical Examiners in the USA. If it appears beside a dark title bar, all subsequent subheadings should be considered key topics.</td>
</tr>
<tr>
<td>🔮</td>
<td>Clinical Pearl</td>
<td>This icon is found in sidebars of the text. It identifies concise, important information which will aid in the diagnosis or management of conditions discussed in the accompanying text.</td>
</tr>
<tr>
<td>🧠</td>
<td>Memory Aid</td>
<td>This icon is found in sidebars of the text. It identifies helpful mnemonic devices and other memory aids.</td>
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<tr>
<td>⚠️</td>
<td>Clinical Flag</td>
<td>This icon is found in sidebars of the text. It indicates information or findings that require urgent management or specialist referral.</td>
</tr>
<tr>
<td>📕</td>
<td>Cross-Reference</td>
<td>This icon is found in sidebars of the text. It indicates a cross-reference for information that is discussed in a separate chapter.</td>
</tr>
<tr>
<td>🔎</td>
<td>Evidence Based Medicine</td>
<td>This icon is found in sidebars of the text. It identifies key research studies for evidence-based clinical decision making related to topics discussed in the accompanying text.</td>
</tr>
<tr>
<td>📲</td>
<td>Colour Photo Atlas</td>
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Chapter Divisions

To aid in studying and finding relevant material quickly, each chapter is organized in the following general framework:

**Basic Anatomy/Physiology Review**
- features the high-yield, salient background information students are often assumed to have remembered from their early medical school education

**Common Differential Diagnoses**
- aims to outline a clinically useful framework to tackle the common presentations and problems faced in the area of expertise

**Diagnoses**
- the bulk of the book
- etiology, epidemiology, pathophysiology, clinical features, investigations, management, complications, and prognosis

**Common Medications**
- a quick reference section for review of medications commonly prescribed
# Common Unit Conversions

To convert from the conventional unit to the SI unit, **multiply** by conversion factor
To convert from the SI unit to the conventional unit, **divide** by conversion factor

<table>
<thead>
<tr>
<th>Conventional Unit</th>
<th>Conversion Factor</th>
<th>SI Unit</th>
</tr>
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<tr>
<td>ACTH pg/mL</td>
<td>0.22</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Albumin g/dL</td>
<td>10</td>
<td>g/L</td>
</tr>
<tr>
<td>Bilirubin mg/dL</td>
<td>17.1</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Calcium mg/dL</td>
<td>0.25</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Cortisol µg/dL</td>
<td>27.59</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Creatinine mg/dL</td>
<td>88.4</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Creatinine clearance mL/min</td>
<td>0.0167</td>
<td>mL/s</td>
</tr>
<tr>
<td>Ethanol mg/dL</td>
<td>0.217</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Ferritin ng/mL</td>
<td>2.247</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Glucose mg/dL</td>
<td>0.0555</td>
<td>mmol/L</td>
</tr>
<tr>
<td>HbA1c %</td>
<td>0.01</td>
<td>proportion of 1.0</td>
</tr>
<tr>
<td>Hemoglobin g/dL</td>
<td>10</td>
<td>g/L</td>
</tr>
<tr>
<td>HDL cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Iron, total µg/dL</td>
<td>0.179</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Lactate (lactic acid) mg/dL</td>
<td>0.111</td>
<td>mmol/L</td>
</tr>
<tr>
<td>LDL cholesterol mg/dL</td>
<td>0.0259</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Leukocytes x 10³ cells/mm³</td>
<td>1</td>
<td>x 10⁹ cells/L</td>
</tr>
<tr>
<td>Magnesium mg/dL</td>
<td>0.411</td>
<td>mmol/L</td>
</tr>
<tr>
<td>MCV µm³</td>
<td>1</td>
<td>fL</td>
</tr>
<tr>
<td>Platelets x 10³ cells/mm³</td>
<td>1</td>
<td>x 10⁹ cells/L</td>
</tr>
<tr>
<td>Reticulocytes % of RBCs</td>
<td>0.01</td>
<td>proportion of 1.0</td>
</tr>
<tr>
<td>Salicylate mg/L</td>
<td>0.00724</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Testosterone ng/dL</td>
<td>0.0347</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄) ng/dL</td>
<td>12.87</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Total Iron Binding Capacity µg/dL</td>
<td>0.179</td>
<td>µmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃) pg/dL</td>
<td>0.0154</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Triglycerides mg/dL</td>
<td>0.0113</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Urea nitrogen mg/dL</td>
<td>0.357</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Uric acid mg/dL</td>
<td>59.48</td>
<td>µmol/L</td>
</tr>
</tbody>
</table>

Celsius → Fahrenheit  
\[ F = (C \times 1.8) + 32 \]

Fahrenheit → Celsius  
\[ C = (F – 32) \times 0.5555 \]

Kilograms → Pounds  
1 kg = 2.2 lbs

Pounds → Ounces  
1 lb = 16 oz

Ounces → Grams  
1 oz = 28.3 g

Inches → Centimetres  
1 in = 2.54 cm
## Commonly Measured Laboratory Values

### Arterial Blood Gases

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>7.35-7.45</td>
</tr>
<tr>
<td>PCO₂</td>
<td>35-45 mmHg</td>
<td>4.7-6.0 kPa</td>
</tr>
<tr>
<td>PO₂</td>
<td>80-105 mmHg</td>
<td>10.6-14 kPa</td>
</tr>
</tbody>
</table>

### Serum Electrolytes

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bicarbonate</td>
<td>22-28 mEq/L</td>
<td>22-28 mmol/L</td>
</tr>
<tr>
<td>Calcium</td>
<td>8.4-10.2 mg/dL</td>
<td>2.1-2.5 mmol/L</td>
</tr>
<tr>
<td>Chloride</td>
<td>95-106 mEq/L</td>
<td>95-106 mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.3-2.1 mEq/L</td>
<td>0.65-1.05 mmol/L</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.7-4.5 mg/dL</td>
<td>0.87-1.45 mmol/L</td>
</tr>
<tr>
<td>Potassium</td>
<td>3.5-5.0 mEq/L</td>
<td>3.5-5.0 mmol/L</td>
</tr>
<tr>
<td>Sodium</td>
<td>136-145 mEq/L</td>
<td>136-145 mmol/L</td>
</tr>
</tbody>
</table>

### Serum Nonelectrolytes

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>3.5-5.0 g/dL</td>
<td>35-50 g/L</td>
</tr>
<tr>
<td>ALP</td>
<td>35-100 U/L</td>
<td>35-100 U/L</td>
</tr>
<tr>
<td>ALT</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Amylase</td>
<td>25-125 U/L</td>
<td>25-125 U/L</td>
</tr>
<tr>
<td>AST</td>
<td>8-20 U/L</td>
<td>8-20 U/L</td>
</tr>
<tr>
<td>Bilirubin (direct)</td>
<td>0-0.3 mg/dL</td>
<td>0-5 μmol/L</td>
</tr>
<tr>
<td>Bilirubin (total)</td>
<td>0.1-1.0 mg/dL</td>
<td>2-17 μmol/L</td>
</tr>
<tr>
<td>BUN</td>
<td>7-18 mg/dL</td>
<td>2.5-7.1 mmol/L</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>&lt;200 mg/dL</td>
<td>&lt;5.2 mmol/L</td>
</tr>
<tr>
<td>Creatinine (female)</td>
<td>10-70 U/L</td>
<td>10-70 U/L</td>
</tr>
<tr>
<td>Creatinine (male)</td>
<td>25-90 U/L</td>
<td>25-90 U/L</td>
</tr>
<tr>
<td>Creatine Kinase – MB fraction</td>
<td>0-12 U/L</td>
<td>0-12 U/L</td>
</tr>
<tr>
<td>Ferritin (female)</td>
<td>12-150 ng/mL</td>
<td>12-150 μg/L</td>
</tr>
<tr>
<td>Ferritin (male)</td>
<td>15-200 ng/mL</td>
<td>15-200 μg/L</td>
</tr>
<tr>
<td>Glucose (fasting)</td>
<td>70-110 mg/dL</td>
<td>3.8-6.1 mmol/L</td>
</tr>
<tr>
<td>HbA1c</td>
<td>&lt;6%</td>
<td>&lt;0.06</td>
</tr>
<tr>
<td>LDH</td>
<td>100-250 U/L</td>
<td>100-250 U/L</td>
</tr>
<tr>
<td>Osmolality</td>
<td>275-300 mOsm/kg</td>
<td>275-300 mOsm/kg</td>
</tr>
</tbody>
</table>

### Serum Hormones

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH (0800h)</td>
<td>&lt;60 pg/mL</td>
<td>&lt;13.2 pmol/L</td>
</tr>
<tr>
<td>Cortisol (0800h)</td>
<td>5-23 μg/dL</td>
<td>138-635 nmol/L</td>
</tr>
<tr>
<td>Prolactin</td>
<td>&lt;20 ng/mL</td>
<td>&lt;20 ng/mL</td>
</tr>
<tr>
<td>Testosterone (male, free)</td>
<td>9-30 ng/dL</td>
<td>0.31-1 pmol/L</td>
</tr>
<tr>
<td>Thyroxine (T₄)</td>
<td>5-12 ng/dL</td>
<td>64-155 nmol/L</td>
</tr>
<tr>
<td>Triiodothyronine (T₃)</td>
<td>115-190 ng/dL</td>
<td>1.8-2.9 mmol/L</td>
</tr>
<tr>
<td>TSH</td>
<td>0.5-5 μU/mL</td>
<td>0.5-5 μU/mL</td>
</tr>
</tbody>
</table>

### Hematologic Values

<table>
<thead>
<tr>
<th>Test</th>
<th>Conventional Units</th>
<th>SI Units</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR (female)</td>
<td>0-20 mm/h</td>
<td>0-20 mm/h</td>
</tr>
<tr>
<td>ESR (male)</td>
<td>0-15 mm/h</td>
<td>0-15 mm/h</td>
</tr>
<tr>
<td>Hemoglobin (female)</td>
<td>12.3-15.7 g/dL</td>
<td>123-157 g/L</td>
</tr>
<tr>
<td>Hemoglobin (male)</td>
<td>13.5-17.5 g/dL</td>
<td>140-174 g/L</td>
</tr>
<tr>
<td>Hematocrit (female)</td>
<td>36-46%</td>
<td>36-46%</td>
</tr>
<tr>
<td>Hematocrit (male)</td>
<td>41-53%</td>
<td>41-53%</td>
</tr>
<tr>
<td>INR</td>
<td>1.0-1.1</td>
<td>1.0-1.1</td>
</tr>
<tr>
<td>Leukocytes</td>
<td>4.5-11 x 10³ cells/mm³</td>
<td>4.5-11 x 10⁹ cells/L</td>
</tr>
<tr>
<td>MCV</td>
<td>88-100 μm³</td>
<td>88-100 fl</td>
</tr>
<tr>
<td>Platelets</td>
<td>150-400 x 10³/mm³</td>
<td>150-400 x 10⁹/L</td>
</tr>
<tr>
<td>PTT</td>
<td>25-35 s</td>
<td>25-35 s</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>0.5-1.5% of RBC</td>
<td>20-84 x 10⁹/L</td>
</tr>
</tbody>
</table>
Ethical, Legal, and Organizational Medicine

Yang Lei, chapter editor
Lindsey Chapman and Meghna Rajaprakash, associate editors
Shany Gertzbein, EBM editor
Dr. Philip C. Hébert, staff editor

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Legal Foundation
History of the Canadian Health Care System
Health Care Expenditure and Delivery in Canada
Physician Licensure and Certification
Role of Professional Associations

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Consent and Capacity
Negligence
Truth-Telling
Ethical Issues in Health Care
Reproductive Technologies
End-of-Life Care
Physician Competence and Professional Conduct
Research Ethics
Physician-Industry Relations
Resource Allocation
Conscientious Objection

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Further information on these topics can be found in the Objectives of the Considerations of the Legal, Ethical and Organizational Aspects of the Practice of Medicine (CLEO) – which can be downloaded free of charge from the Medical Council of Canada website at http://mcc.ca/wp-content/uploads/CLEO.pdf

Canadian law applicable to medical practice varies between jurisdictions and changes over time. Criminal law is nationwide, but non-criminal (civil) law varies between provinces. This section is meant to serve only as a guide. Students and physicians should ensure that their practices conform to local and current laws.

Acronyms

AE adverse event
ART advanced reproductive technologies
CAIR Canadian Association of Interns and Residents
CFMS Canadian Federation of Medical Students
CFPC College of Family Physicians of Canada
CMA Canadian Medical Association
CME continuing medical education
CMPA Canadian Medical Protective Association
CPSP College of Physicians and Surgeons of Ontario
EMR electronic medical record
FMEQ Fédération médicale étudiante du Québec
FRFC Fellow of the Royal College of Physicians of Canada
FRSC Fellow of the Royal College of Surgeons of Canada
GA gestational age
GDP gross domestic product
HCCA Health Care Consent Act
INF in vitro fertilization
LMCC Licentiate of the Medical Council of Canada
MCC Medical Council of Canada
OECD Organization for Economic Co-operation and Development
OMA Ontario Medical Association
OTC over the counter
PHO Provincial Housestaff Organization
PIPEDA Personal Information Protection and Electronic Documents Act
POA power of attorney
PTMA Provincial/Territorial Medical Association
RCPSC Royal College of Physicians and Surgeons of Canada
SDM substitute decision-maker
The Canadian Health Care System

Overview of Canadian Health Care System

- one federal, three territorial, and ten provincial systems
- major complexities involved in establishment of Canadian health policy include geographical diversity, socioeconomic divisions, and international pressures
- financed by both the public (70%) and private (30%) sectors
- each provincial plan must cover all medically necessary health services delivered in hospitals and by physicians; may choose to cover services such as home care and prescription drugs
- non-insured health services and fees are either covered by private insurance or by the individual
- workers' compensation funds cover treatment for work-related injuries and diseases

Table 1. Division of Government Responsibilities in Health Care

<table>
<thead>
<tr>
<th>Federal Government</th>
<th>Provincial Government</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Marine hospitals and quarantine (Constitution Act, 1867)</td>
<td>- Establishment, maintenance and management of hospitals, asylums, charities, and charitable institutions (Constitution Act, 1867)</td>
</tr>
<tr>
<td>- Health care services for Aboriginal people, federal government employees (RCMP and armed forces), immigrants, and civil aviation personnel</td>
<td>- Licensing of physicians, nurses and other health professionals</td>
</tr>
<tr>
<td>- Investigations into public health</td>
<td>- Determining the standards for licensing all hospitals</td>
</tr>
<tr>
<td>- Regulation of food and drugs</td>
<td>- Administering provincial medical insurance plans</td>
</tr>
<tr>
<td>- Inspection of medical devices</td>
<td>- Financing health care facilities</td>
</tr>
<tr>
<td>- Administration of health care insurance</td>
<td>- Delivery of certain public health services</td>
</tr>
<tr>
<td>- General information services related to health conditions and practices</td>
<td></td>
</tr>
<tr>
<td>- Role in health derived from government’s constitutional powers over criminal law (basis for legislation such as Food and Drugs Act and Controlled Substances Act), spending, and ‘peace, order, and good government’</td>
<td></td>
</tr>
</tbody>
</table>

Legal Foundation

- the legal foundation of the Canadian health system is based on two constitutional documents:
  1. Constitution Act (1867): deals primarily with the jurisdictional power between federal and provincial governments
  2. The Canadian Charter of Rights and Freedoms (1982): does not guarantee a right to health care but, given government’s decision to finance health care, they are constitutionally obliged to do so consistently with the rights and freedoms outlined in the Charter (including the right to equality, physicians’ mobility rights, etc.)

- and two statutes:
  1. Canada Health Act (1984): outlines the national terms and conditions that provincial health systems must meet in order to receive federal transfer payments
  2. Canada Health and Social Transfer Act (1996): federal government gives provinces a single grant for health care, social programs, and post-secondary education; division of resources at provinces’ discretion

History of the Canadian Health Care System

1867  British North America Act (now Constitution Act) establishes Canada as a confederacy
- “establishment, maintenance, and management of hospitals” under provincial jurisdiction

1965  Royal Commission on Health Services (Hall Commission) recommends federal leadership and financial support with provincial government operation

1984  Canada Health Act passed by federal government
- replaces Medical Care Act (1966) and Hospital Insurance and Diagnostic Services Act (1957)
- provides federal funds to provinces with universal hospital insurance
- maintains federal government contribution at 50% on average, with poorer provinces receiving more funds
- medical insurance must be ‘comprehensive, portable, universal, and publicly administered’
- bans extra-billing by new fifth criterion: accessibility
1996 *Canada Health and Social Transfer Act* passed by federal government
- federal government gives provinces a single grant for health care, social programs, and
  post-secondary education; division of resources at provinces' discretion

2001 *Kirby and Romanow Commissions* appointed
  *Kirby Commission* (final report, October 2002)
- examines history of health care system in Canada, pressures and constraints of current
  health care system, role of federal government, and health care systems in foreign
  jurisdictions
  *Romanow Commission* (final report, November 2002)
- dialogue with Canadians on the future of Canada's public health care system

2004 *First Ministers' Meeting on the Future of Health Care* produces a 10 year plan
- priorities include reductions in waiting times, development of a national pharmacare
  plan, and primary care reform

2005 *Chaoulli v. Quebec*, Supreme Court of Canada decision
- rules that Quebec's banning of private insurance is unconstitutional under the
  Quebec Charter of Rights, given that patients do not have access to those services under
  the public system in a timely way

2004 *First Ministers' Meeting on the Future of Health Care* produces a 10 year plan
- priorities include reductions in waiting times, development of a national pharmacare
  plan, and primary care reform

2005 *Chaoulli v. Quebec*, Supreme Court of Canada decision
- rules that Quebec's banning of private insurance is unconstitutional under the
  Quebec Charter of Rights, given that patients do not have access to those services under
  the public system in a timely way

2011 First progress report by the Health Council reviews progress (2004 First Ministers'
10 year plan)
- significant reductions in wait times for specific areas (such as cancer, joint replacement
  and sight restoration), but may have inadvertently caused increases in wait times of
  other services
- despite large investments into EMRs, Canada continues to have very low uptake,
  ranking last in the Commonwealth Fund International Health Policy survey, with only
  37% use among primary care physicians
- little progress in creating a national strategy for equitable access to pharmaceuticals;
  however, there has been some success in increasing pharmacists' scope of practice,
  reducing generic drugs costs, and implementing drug info systems
- increases in funding to provinces at 6% per annum until the 2016-2017 fiscal year;
  from then onwards, increases tied to nominal GDP at a minimum of 3% per annum

2012 Second progress report by the Health Council reviews progress towards 2004 First
Ministers' 10 year plan
- funding is sufficient; however, more innovation is needed including incentivizing
  through models of remuneration
- 46 recommendations made to address the lack of progress

2014 Expiry of current 10 Year Health Care Funding Agreement between federal and
provincial governments

---

**Health Care Expenditure and Delivery in Canada**

- projected total health care expenditure in 2014 was $214.9 billion, 11% of the GDP,
  approximately $6,045 CDN per person
- increasing rate of growth in health spending, surpassing rate of inflation and population growth
  in Canada
- increase in health care costs attributed by some to the increasing number of physicians, and the
  extent and level of services they provide for each patient annually

**Sources of Health Care Funding**
- 70.5% of healthcare spending came from public sector sources in 2014, compared to the US at
  47.8% (OECD average: 73.3%)
- public sector covers services offered on a fee-for-service basis in physicians' offices and in
  hospitals
- public sector does not cover services provided by privately practicing health professionals
  (e.g. dentists, chiropractors, optometrists, massage therapists, osteopaths, physiotherapists,
  podiatrists, psychologists, private duty nurses, and naturopaths), prescription drugs, OTC
  drugs, personal health supplies, and use of residential care facilities
Delivery of Health Care

- Hospital services in Canada are publicly funded but delivered through private, not-for-profit institutions owned and operated by communities, religious organizations, and regional health authorities.
- Other countries, such as the United States (a mix of public and private funding, as well as private for-profit and private not-for-profit delivery) and the United Kingdom (primarily public funding and delivery) have different systems of delivery.

### Physician Licensure and Certification

- Physician certification is governed nationally, while the medical profession in Canada self-regulates under the authority of provincial legislation.
- Self-regulation is based on the premise that the licensing authority must act first and foremost in the interest of the public.

#### Table 2. Key Physician Certification and Licensing Bodies in Canada

<table>
<thead>
<tr>
<th>Certifying Body</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>MCC</td>
<td>Certifies physicians with the LMCC. The LMCC is acquired by passing the MCC Qualifying Examination Parts I and II</td>
</tr>
<tr>
<td>RCPSC</td>
<td>Certifies specialists who complete an accredited residency program and pass the appropriate exam. Voluntary membership of the RCPSC is designated FRCPC or FRCSC</td>
</tr>
<tr>
<td>CFPC</td>
<td>Certifies family physicians who complete an accredited residency program and pass the Certification Examination in Family Medicine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Licensing Body</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPSO</td>
<td>Membership to the provincial licensing authority is mandatory. Licensing authority functions include: • Provide non-transferable licensure to physicians • Maintaining ethical, legal, and competency standards and developing policies to guide doctors • Investigating complaints against doctors • Disciplining doctors guilty of professional misconduct or incompetence • At times of license investiture and renewal, physicians must disclose if they have a condition (such as HIV positivity, drug addiction, or other illnesses that may impact their ability to practice safely)</td>
</tr>
</tbody>
</table>

- The RCPSC and CFPC are responsible for monitoring ongoing CME and professional development.
- Certification by the LMCC plus either the RCPSC or CFPC is a minimum requirement for licensure by most provincial licensing authorities.
Role of Professional Associations

Table 3. Key Professional Associations

<table>
<thead>
<tr>
<th>Association</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMA</td>
<td>Provides leadership to doctors and advocates for access to high quality care in Canada</td>
</tr>
<tr>
<td></td>
<td>Represents physician and population concerns at the national level</td>
</tr>
<tr>
<td></td>
<td>Membership is voluntary</td>
</tr>
<tr>
<td>OMA and Other PTMAs</td>
<td>Negotiates fee and benefit schedules with provincial governments</td>
</tr>
<tr>
<td></td>
<td>Represents the economic and professional interests of doctors</td>
</tr>
<tr>
<td></td>
<td>Membership is voluntary</td>
</tr>
<tr>
<td>CMPA</td>
<td>Physician-run organization that protects the integrity of member physicians</td>
</tr>
<tr>
<td></td>
<td>Provides legal defence against allegations of malpractice or negligence</td>
</tr>
<tr>
<td></td>
<td>Provides risk management and educational programs</td>
</tr>
<tr>
<td></td>
<td>Membership is voluntary</td>
</tr>
<tr>
<td>CAIR and PHO</td>
<td>Upholds economic and professional interests of residents across Canada</td>
</tr>
<tr>
<td></td>
<td>Facilitates discussion amongst PHOs regarding policy and advocacy items</td>
</tr>
<tr>
<td>CMFS and FMÉQ</td>
<td>Medical students are represented at their universities by student bodies, which collectively form the</td>
</tr>
<tr>
<td></td>
<td>CFMS or FMÉQ</td>
</tr>
<tr>
<td></td>
<td>The FMÉQ membership includes that of francophone medical schools</td>
</tr>
</tbody>
</table>

Ethical and Legal Issues in Canadian Medicine

Introduction to the Principles of Ethics

- ethics addresses
  1. principles and values that help define what is morally right and wrong
  2. rights, duties and obligations of individuals and groups
- the practice of medicine assumes there is one code of professional ethics for all doctors and that they will be held accountable by that code and its implications
- the doctor-patient relationship is formed on trust, which is recognized in the concept of fiduciary duty/responsibility of physician towards patient
  - a fiduciary duty is a legal duty to act solely in another party's interest; one may not profit from the relationship with principals unless he/she has the principal's express consent

Table 4. The Four Principles Approach to Medical Ethics

<table>
<thead>
<tr>
<th>Principle</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autonomy</td>
<td>Recognizes an individual’s right and ability to decide for himself/herself according to his/her beliefs and values</td>
</tr>
<tr>
<td></td>
<td>Not applicable in situations where informed consent and choice are not possible or may not be appropriate</td>
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<tr>
<td>Beneficence</td>
<td>The patient-based ‘best interests’ standard that combines doing good, avoiding harm, taking into account the patient’s values, beliefs, and preferences, so far as these are known</td>
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<tr>
<td></td>
<td>Autonomy should be integrated with the physician’s conception of a patient’s medically-defined best interests</td>
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<tr>
<td></td>
<td>The aim is to minimize harmful outcomes and maximize beneficial ones</td>
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<td></td>
<td>Paramount in situations where consent/choice is not possible or may not be appropriate</td>
</tr>
<tr>
<td>Non-Maleficence</td>
<td>Obligation to avoid causing harm; primum non nocere (“First, do no harm”)</td>
</tr>
<tr>
<td></td>
<td>A limit condition of the Beneficence principle</td>
</tr>
<tr>
<td>Justice</td>
<td>Fair distribution of benefits and harms within a community, regardless of geography or privilege</td>
</tr>
<tr>
<td></td>
<td>Concept of fairness: Is the patient receiving what he/she deserves – is his/her fair share? Is he/she treated the same as equally situated patients? How does one set of treatment decisions impact others?</td>
</tr>
<tr>
<td></td>
<td>Basic human rights, such as freedom from persecution and the right to have one’s interests considered and respected</td>
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</tbody>
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CMA Code of Ethics

- The CMA developed a Code of Ethics that acts as a common ethical framework for Canadian physicians. The Code of Ethics is:
  - prepared by physicians for physicians and applies to physicians, residents, and medical students
  - based on the fundamental ethical principles of medicine
  - sources include the Hippocratic Oath, developments in human rights, recent bioethical discussion
  - CMA policy statements address specific ethical issues not mentioned by the code (e.g. abortion, transplantation, and euthanasia)
Confidentiality

Overview of Confidentiality
- a full and open exchange of information between patient and physician is central to a therapeutic relationship
- privacy is the right of patients (which they may forego) while confidentiality is the duty of doctors (which they must respect barring patient consent or the requirements of the law)
- if inappropriately breached by a doctor, he/she can be sanctioned by the hospital, court, or regulatory authority
- based on the ethical principle of patient autonomy, patients have the right to the following:
  - control of their own information
  - the expectation that information concerning them will receive proper protection from unauthorized access by others (see Privacy of Medical Records, below)
- confidentiality may be ethically and legally breached in certain circumstances (e.g. the threat of harm to others)
- unlike the solicitor-client privilege, there is no ‘physician-patient privilege’ by which a physician, even a psychiatrist, can promise the patient absolute confidentiality
- physicians should seek advice from their local health authority or the CMPA before disclosing HIV status of a patient to someone else
  - many jurisdictions make mandatory not only the reporting of serious communicable diseases (e.g. HIV), but also the reporting of those who harbour the agent of the communicable disease
  - physicians failing to abide by such regulations could be subject to professional or civil actions
- the legal duty to maintain patient confidentiality is imposed by provincial health information legislation and precedent-setting cases in the common law

Statutory Reporting Obligations
- legislation has defined specific instances where public interest overrides the patient’s right to confidentiality; varies by province, but may include
  1. suspected child abuse or neglect – report to local child welfare authorities (e.g. Children’s Aid Society)
  2. fitness to drive a vehicle or fly an airplane – report to provincial Ministry of Transportation (see Geriatric Medicine, GM11)
  3. communicable diseases – report to local public health authority (see Population Health and Epidemiology, PH26)
  4. improper conduct of other physicians or health professionals – report to College or regulatory body of the health professional (sexual impropriety by physicians is required reporting in some provinces)
  5. vital statistics must be reported; reporting varies by province (e.g. in Ontario, births are required to be reported within 30 days to Office of Registrar General or local municipality; death certificates must be completed by a MD then forwarded to municipal authorities)
  6. reporting to coroners (see Physician Responsibilities Regarding Death, ELOAM14)
- physicians who fail to report in these situations are subject to prosecution and penalty, and may be liable if a third party has been harmed

Duty to Protect/Warn
- the physician has a duty to protect the public from a known dangerous patient; this may involve taking appropriate clinical action (e.g. involuntary detention of violent patients for clinical assessment), informing the police, or warning the potential victim(s) if a patient expresses an intent to harm
- first established by a Supreme Court of California decision in 1976 (Tarasoff v. Regents of the University of California); supported by Canadian courts
- obliged by the CMA Code of Ethics and recognized by some provincial/territorial regulatory authorities
- concerns of breaching confidentiality should not prevent the MD from exercising the duty to protect; however, the disclosed information should not exceed that required to protect others
- applies in a situation where
  1. there is a clear risk to identifiable person(s);
  2. there is a risk of serious bodily harm or death; and
  3. the danger is imminent (i.e. more likely to occur than not)

Disclosure for Legal Proceedings
- disclosure of health records can be compelled by a court order, warrant, or subpoena

Privacy of Medical Records
- privacy of health information is protected by professional codes of ethics, provincial and federal legislation, the Canadian Charter of Rights and Freedoms, and the physician’s fiduciary duty
• the federal government created the PIPEDA in 2000 which established principles for the collection, use, and disclosure of information that is part of commercial activity (e.g. physician practices, pharmacies, private labs)
• PIPEDA has been superseded by provincial legislation in many provinces, such as the Ontario Personal Health Information Protection Act, which applies more specifically to health information

Duties of Physicians with Regard to the Privacy of Health Information
• inform patients of information-handling practices through various means (e.g. posting notices, brochures and pamphlets, and/or through discussions with patients)
• obtain the patient's expressed consent to disclose information to third parties
  • under Ontario privacy legislation, the patient's expressed consent need not be obtained to share information between health care team members involved in the 'circle of care.' However, the patient may withdraw consent for this sharing of information and may put part in a 'lock box.'
• provide the patient with access to their entire medical record; exceptions include instances where there is potential for serious harm to the patient or a third party
• provide secure storage of information and implement measures to limit access to patient records
• ensure proper destruction of information that is no longer necessary
• regarding taking pictures or videos of patients, findings, or procedures, in addition to patient consent and privacy laws, trespassing laws apply in some provinces

Consent and Capacity

Ethical Principles Underlying Consent and Capacity
• consent is the autonomous authorization of a medical intervention by a patient
• usually the principle of respect for patient autonomy overrides the principle of beneficence
• where a patient cannot make an autonomous decision (i.e. incapable), it is the duty of the SDM (or the physician in an emergency) to act on the patient's known prior wishes or, failing that, to act in the patient's best interests
• there is a duty to discover, if possible, what the patient would have wanted when capable
• central to determining best interests is understanding the patient's values, beliefs, and cultural or religious background
• more recently expressed wishes take priority over remote ones
• patient wishes may be verbal or written
• patients found incapable to make a specific decision should still be involved in that decision as much as possible
• agreement or disagreement with medical advice does not determine findings of capacity/incapacity
• however, patients opting for care that puts them at risk of serious harm that most people would want to avoid should have their capacity carefully assessed

Four Basic Requirements of Valid Consent
1. Voluntary
   • consent must be given free of coercion or pressure (e.g. from parents or other family members who might exert 'undue influence')
   • the physician must not deliberately mislead the patient about the proposed treatment
2. Capable
   • the patient must be able to understand and appreciate the nature and effect of the proposed treatment
3. Specific
   • the consent provided is specific to the procedure being proposed and to the provider who will carry out the procedure (e.g. the patient must be informed if students will be involved in providing the treatment)
4. Informed
   • sufficient information and time must be provided to allow the patient to make choices in accordance with his/her wishes, including
     • the nature of the treatment or investigation proposed and its expected effects
     • all significant risks and special or unusual risks
     • alternative treatments or investigations and their anticipated effects and significant risks
     • the consequences of declining treatment
     • risks that are common sense need not be disclosed (i.e. bruising after venipuncture)
     • answers to any questions the patient may have
   • the reasonable person test – the physician must provide all information that would be needed "by a reasonable person in the patient's position" to be able to make a decision
   • disclose common adverse events (>1/200 chance of occurrence) and serious risks (e.g. death), even if remote
   • it is the physician's responsibility to make reasonable attempts to ensure that the patient understands the information
   • physicians should not withhold information about a legitimate therapeutic option based on personal conscience (e.g. not discussing the option of emergency contraception)
Obtaining Legal Consent

- Consent of the patient must be obtained before any medical intervention is provided; consent can be:
  - verbal or written, although written is usually preferred
  - implied (e.g., a patient holding out their arm for an immunization) or expressed
- Consent is an ongoing process and can be withdrawn or changed after it is given, unless stopping a procedure would put the patient at risk of serious harm
- HCAA of Ontario (1996) covers consent to treatment, admission to a facility, and personal assistance services (e.g., home care)

Exceptions to Consent

1. Emergencies
   - Treatment can be provided without consent where a patient is experiencing severe suffering, or where a delay in treatment would lead to serious harm or death and consent cannot be obtained from the patient or their SDM
   - Emergency treatment should not violate a prior expressed wish of the patient (e.g., a signed Jehovah’s Witness card)
   - If patient is incapable, MD must document reasons for incapacity and why situation is emergent
   - If there is no SDM for the incapable patient, the doctor can apply to the CCB to appoint a patient representative

2. Legislation
   - Mental Health legislation allows for:
     - the detention of patients without their consent
     - psychiatric outpatients may be required to adhere to a care plan in accordance with Community Treatment Orders (see Psychiatry, PS55)
• Public Health legislation allows medical officers of health to detain, examine, and treat patients without their consent (e.g. a patient with TB refusing to take medication) to prevent transmission of communicable diseases

3. Special Situations
• public health emergencies (e.g. an epidemic or communicable disease treatment)
• warrant for information by police

Consequences of Failure to Obtain Valid Consent
• treatment without consent is battery (an offense in tort), even if the treatment is life-saving (excluding situations outlined in exceptions section above)
• treatment of a patient on the basis of poorly informed consent may constitute negligence, also an offense in tort
• the onus of proof that valid consent was not obtained rests with the plaintiff (usually the patient)

Overview of Capacity
• capacity is the ability to:
  1. understand information relevant to a treatment decision
  2. appreciate the reasonably foreseeable consequences of a decision or lack of a decision
• capacity can change over time (e.g. temporary incapacity secondary to delirium)
• most Canadian jurisdictions distinguish capacity to make health care decisions from capacity to make financial decisions; a patient may be deemed capable of one, but not the other
• a person is presumed capable unless there is good evidence to the contrary
• capable patients are entitled to make their own decisions
• capable patients can refuse treatment even if it leads to serious harm or death; however, decisions that put patients at risk of serious harm or death require careful scrutiny

Assessment of Capacity
• capacity assessments must be conducted by a physician and, if appropriate, in consultation with other health care professionals (e.g. another physician, a mental health nurse)
• clinical capacity assessment may include
  1. specific capacity assessment (i.e. capacity specific to the decision at hand)
     1. effective disclosure of information and evaluation of patient’s reason for decision
     2. understanding of
        – his/her condition
        – the nature of the proposed treatment
        – alternatives to the treatment
        – the consequences of accepting and rejecting the treatment
        – the risks and benefits of the various options
     3. for the appreciation needed for decision making capacity, a person must
        – acknowledge the condition that affects him/herself
        – be able to assess how the various options would affect him or her
        – be able to reach a decision and adhere to it, and make a choice, not based primarily upon delusional belief
  2. general impressions
  3. input from psychiatrists, neurologists, etc.
• employ “Aid to Capacity Evaluation”
• a decision of incapacity may warrant further assessment by psychiatrist(s), legal review boards (e.g. in Ontario, the Consent and Capacity Review Board), or the courts
• judicial review is open to patients if found incapable

Treatment of the Incapable Patient in a Non-Emergent Situation
• obtain informed consent from SDM
• an incapable patient can only be detained against his/her will to receive treatment if he/she meets criteria for certification under the Mental Health Act (see Psychiatry, PS54); in such a situation:
  1. document assessment in chart
  2. notify patient of assessment using appropriate Mental Health Form(s) (Form 42 in Ontario)
  3. notify Rights Advisor

Substitute Decision-Makers
• SDMs must follow the following principles when giving informed consent:
  1. values and beliefs held by the patient while capable
  2. whether well-being is likely to improve with vs. without treatment
  3. whether the expected benefit outweighs the risk of harm
• the final decision of the SDM may and should be challenged by the MD if the MD believes the SDM is not abiding by the above principles

Most provinces have legislated hierarchies for SDMs; the hierarchy in Ontario is:
• Legally appointed guardian
• Appointed attorney for personal care, if a power of attorney confers authority for treatment consent (see Powers of Attorney, ELOAM10)
• Representative appointed by the Consent and Capacity Board
• Spouse or partner
• Child (age 16 or older) or parent (unless the patient has only a right of access)
• Public guardian and trustee
Instructional Advance Directives
- allow patients to exert control over his/her care once they are no longer capable
- the patient sets out his/her decisions about future health care, including who he/she would allow
to make treatment decisions on his/her behalf and what types of interventions he/she would want
- takes effect once the patient is incapable with respect to treatment decisions
- in Ontario, a person can appoint a power of attorney for personal care to carry out his/her
advance directives
- patients should be encouraged to review these documents with their family and physicians and
to reevaluate them often to ensure they are current with their wishes

POWERS OF ATTORNEY
- all Guardians and Attorneys have fiduciary duties for the dependent person

Definitions
- Power of Attorney for Personal Care
  - a legal document in which one person gives another the authority to make personal care
decisions (health care, nutrition, shelter, clothing, hygiene, and safety) on their behalf if they
become mentally incapable
- Guardian of the Person
  - someone who is appointed by the Court to make decisions on behalf of an incapable person
in some or all areas of personal care, in the absence of a POA for personal care
- Continuing Power of Attorney for Property
  - a legal document in which a person gives another the legal authority to make decisions about
their finances if they become unable to make those decisions
- Guardian of Property
  - someone who is appointed by the Public Guardian and Trustee or the Courts to look after an
incapable person's property or finances
- Public Guardian and Trustee
  - acts as a SDM of last resort on behalf of mentally incapable people who do not have another
individual to act on their behalf
- Pediatric Aspects of Capacity Covered
  - no age of consent in all provinces and territories except Quebec; consent depends on
patient's decision-making capacity
  - Quebec has a specific age of consent, but common law and case law deem underage legal
minors capable, allowing them to make their own choices
  - infants and children are assumed to lack mature decision-making capacity for consent
  - but they should still be involved (i.e. be provided with information appropriate to their
comprehension level)
  - adolescents are usually treated as adults
  - preferably, assent should still be obtained from patient, even if not capable of giving consent
  - in the event that the physician believes the SDM is not acting in the child's best interests, an
appeal must be made to the local child welfare authorities
  - under normal circumstances, parents have right of access to the child's medical record

Negligence

Ethical Basis
- the doctor-patient relationship is formed on trust, which is recognized in the concept of
fiduciary duty/responsibility of physician towards patient
- a fiduciary duty is a legal duty to act solely in another party's interest and may not profit from
relationship with principals unless they have the principals express consent
- negligence or malpractice is a form of failure on the part of the physician in fulfilling his/her
fiduciary duty in providing appropriate care and leading to harm of the patient (and/or abuse of
patient's trust)

Legal Basis
- physicians are legally liable to their patients for causing harm (tort) through a failure to meet the
standard of care applicable under the circumstances
- standard/duty of care is defined as one that would reasonably be expected under similar
circumstances of an ordinary, prudent physician of the same training, experience, specialization,
and standing
- liability arises from physician's common law duty of care to his/her patients in the doctor/patient
relationship (or, in Quebec, from the Civil Code provisions regarding general civil liability)
- action(s) in negligence (or civil liability) against a physician must be launched by a patient
within a specific prescribed period required by the respective province in which the actions
occurred

- there is no age of consent in Ontario. Capacity is assessed on an individual basis
- errors of care are compatible with non-negligent care if they are ones that
  a reasonably cautious and skilled MD
  could make (i.e. mistakes can be made
due to 'honest error')
- there are four basic elements for action against a
  physician to succeed in negligence:
  1. A duty of care owed to the patient
     (i.e. doctor/patient relationship must
     be established)
  2. A breach of the standard of care
  3. Some harm or injury to the patient
  4. The harm or injury must have been
causally caused by the breach of the duty of care
Truth-Telling

Ethical Basis
• helps to promote and maintain a trusting physician-patient relationship
• patients have a right to be told important information that physicians have regarding their care
• enables patients to make informed decisions about health care and their lives

Legal Basis
• required for valid patient consent (see Consent and Capacity, ELOAM7)
  ▪ goal is to disclose information that a reasonable person in the patient’s position would need in order to make an informed decision (“standard of disclosure”)
• withholding information can be a breach of fiduciary duty and duty of care
• obtaining consent on the basis of misleading information can be seen as negligent

Evidence about Truth-Telling
• most patients want to know what is wrong with them
• although many patients want to protect family members from bad news, they themselves would want to be informed in the same situation
• truth-telling improves adherence and health outcomes
• informed patients are more satisfied with their care
• negative consequences of truth-telling can include decreased emotional well-being, anxiety, worry, social stigmatization, and loss of insurability

Challenges in Truth-Telling
Medical Error
• medical error may be defined as ‘preventable adverse events (AEs)’ caused by the patient’s medical care and not the patient’s underlying illness; some errors may be identified before they harm the patient, so not all error is truly ‘adverse’
• many jurisdictions and professional associations expect and require physicians to disclose medical error; that is, any event that harms or threatens to harm patients must be disclosed to the patient or the patient’s family and reported to the appropriate health authorities
• physicians should disclose to patients the occurrence of AEs or errors caused by medical management, but should not suggest that they resulted from negligence because:
  ▪ negligence is a legal determination
  ▪ error is not equal to negligence (see Negligence, ELOAM10)
• disclosure allows the injured patient to seek appropriate corrective treatment promptly
• physicians should avoid simple attributions as to cause and sole responsibility of others or oneself
• physicians should offer apologies or empathic expressions of regret (e.g. “I wish things had turned out differently”) as these can increase trust and are not admissions of guilt or liability
• Apology Acts across Canada protect apologies, both as expressions of regret and admissions of responsibility, from being used as evidence of liability and negligence

Breaking Bad News
• ‘bad news’ may be any information that reveals conditions or illnesses threatening the patient’s sense of well-being
• caution patients in advance of serious tests about possible bad findings
• give warnings of impending bad news (see sidebar for example) and make sure you provide time for the patient
• poorly done disclosure may be as harmful as non-disclosure
• truth-telling may be a process requiring multiple visits
• adequate support should be provided along with the disclosure of difficult news
• SPIKES protocol was developed to facilitate “breaking bad news”

Arguments Against Truth-Telling
• may go against certain cultural norms and expectations
• may lead to patient harm and increased anxiety
• 10-20% of patients prefer not to be informed
• medical uncertainty may result in the disclosure of uncertain or inaccurate information

Exceptions to Truth-Telling
• a patient may waive his/her right to know the truth about their situation (i.e. decline information that would normally be disclosed) when
  ▪ the patient clearly declines to be informed
  ▪ a strong cultural component exists that should be respected and acknowledged
• the patient may wish others to be informed and make the medical decisions for him/her
• the more weighty the consequences for the patient from non-disclosure, the more carefully one must consider the right to ignorance
• ‘emergencies’: an urgent need to treat may legitimately delay full disclosure; the presumption is that most people would want such treatment and the appropriate SDM cannot be found

Protocol to Break Bad News: SPIKES
S Setting the scene and listening skills
P Patient’s perception of condition and seriousness
I Invitation from patient to give information
K Knowledge – giving medical facts
E Explore emotions and empathize
S Strategy and summary
Source: Baile WF, Buckman R. 2000

CPSO Policy on Truth-Telling
Physicians should provide patients with whatever information that will, from the patient’s perspective, have a bearing on medical decision-making and communicate that information in a way that is comprehensible to the patient

Adverse Event
An unintended injury or complication from health care management resulting in disability, death, or prolonged hospital stay

Open Disclosure of AEs: Transparency and Safety in Health Care
Health care providers have a fiduciary duty to disclose AEs to their patients. Professional societies codify medical providers’ ethical requirement to disclose AEs to patients in accordance with the four principles of biomedical ethics. Transparency and honesty in relationships with patients create opportunities for learning that lead to systems improvements in health care organizations. Disclosure invariably becomes a component of broad systems improvement and is closely linked to improving patient safety.

Truth-Telling in Discussing Prognosis in Advanced Life-Limiting Illnesses
Palliat Med 2007;21(6):507-517
Many physicians express discomfort at having to breach the topic of prognosis, including limited life expectancy, and may withhold information or not disclose prognosis.
A systematic review of 46 studies relating to truth-telling in discussing prognosis with patients with progressive, advanced life-limiting illnesses and their caregivers showed that although the majority of physicians believed that patients and caregivers should be told the truth about the prognosis, in practice, many either avoid discussing the topic or withheld information. Reasons include perceived lack of training, stress, no time to attend to the patient’s emotional needs, fear of a negative impact on the patient, uncertainty about prognosis, requests from family members to withhold information and a feeling of inadequacy or hopelessness regarding the unavailability of further curative treatment.
Evidence suggests that patients can discuss the topic without it having a negative impact on them.

Source: Baile WF, Buckman R. 2000
• ‘therapeutic privilege’
  ▪ withholding of information by the clinician in the belief that disclosure of the information
    would itself lead to severe anxiety, psychological distress or physical harm to the patient
  ▪ clinicians should avoid invoking therapeutic privilege due to its paternalistic overtones and is
    a defense of non-disclosure that is rarely accepted anymore
  ▪ it is often not the truth that is unpalatable; it is how it is conveyed that can harm the patient

Ethical Issues in Health Care

Managing Controversial and Ethical Issues in Practice
• discuss in a non-judgmental manner
• ensure patients have full access to relevant and necessary information
• identify if certain options lie outside of your moral boundaries and refer to another physician if
  appropriate
• consult with appropriate ethics committees or boards
• protect freedom of moral choice for students or trainees

Source: MCC-CLEO Objectives 1998

Reproductive Technologies

Overview of the Maternal-Fetal Relationship
• in general, maternal and fetal interests align
• in some situations, a conflict between maternal autonomy and the best interests of the fetus may
  arise

Ethical Issues and Arguments
• principle of reproductive freedom: women have the right to make their own reproductive
  choices
• coercion of a woman to accept efforts to promote fetal well-being is an unacceptable
  infringement of her personal autonomy

Legal Issues and Arguments
• the law upholds a woman's right to life, liberty, and security of person, and does not recognize
  fetal rights; key aspects of the mother's rights include
  ▪ if a woman is competent and refuses medical advice, her decision must be respected even if
    the fetus will suffer
  ▪ the fetus does not have legal rights until it is born alive and with complete delivery from the
    body of the woman

Royal Commission on New Reproductive Technologies (1993) recommendations:
1. medical treatment must never be imposed upon a competent pregnant woman against her
   wishes
2. no law should be used to confine a pregnant woman in the interest of her fetus
3. the conduct of a pregnant woman in relation to her fetus should not be criminalized
4. child welfare should never be used to control a woman's behaviour during pregnancy
5. civil liability should never be imposed upon a woman for harm done to her fetus during
   pregnancy

Examples involving the use of established guidelines
• a woman is permitted to refuse HIV testing during pregnancy, even if vertical transmission to
  fetus results
• a woman is permitted to refuse Caesarean section in labour that is not progressing, despite
  evidence of fetal distress

Advanced Reproductive Therapies
• includes non-coital insemination, hormonal ovarian stimulation, and IVF
• topics with ethical concerns
  ▪ donor anonymity vs. child-centred reproduction (i.e. knowledge about genetic medical
    history)
  ▪ preimplantation genetic testing for diagnosis before pregnancy
  ▪ use of new techniques without patients appreciating their experimental nature
  ▪ embryo status – the Supreme Court of Canada maintains that fetuses are "unique" but not
    persons under law; this view would likely apply to embryos as well
  ▪ access to ART
  ▪ private vs. public funding of ART
  ▪ social factors limiting access to ART (e.g. same-sex couples)
  ▪ the ‘commercialization’ of reproduction

Examples of Warning of Impending Bad News
"I have something difficult to tell you…"
"This may come as a shock to you, but the tests indicate…"
"There is no easy way for me to tell you this, so I will tell you straight away that you have a serious problem…"
**Fetal Tissue**
- pluripotent stem cells can currently be derived from human embryonic and fetal tissue
- potential uses of stem cells in research
  - studying human development and factors that direct cell specialization
  - evaluating drugs for efficacy and safety in human models
  - cell therapy: using stem cells grown *in vitro* to repair or replace degenerated/destroyed/malignant tissues (e.g. Parkinson’s disease)
- genetic treatment aimed at altering somatic cells (e.g. myocardial or immunological cells) is acceptable and ongoing

**Induced Abortion**
- CMA definition of induced abortion: the active termination of a pregnancy before fetal viability (fetus >500 g or >20 wk GA)
- CMA policy on induced abortion
  1. induced abortion should not be used as an alternative to contraception
  2. counselling on contraception must be readily available
  3. full and immediate counselling services must be provided in the event of unwanted pregnancy
  4. there should be no delay in the provision of abortion services
  5. no patient should be compelled to have a pregnancy terminated
  6. physicians should not be compelled to participate in abortion – if morally opposed, the physician should inform the patient so she may consult another physician
  7. no discrimination should be directed towards either physicians who do not perform or assist at induced abortions or physicians who do
  8. induced abortion should be uniformly available to all women in Canada and health care insurance should cover all the costs (note: the upper limit of GA for which coverage is provided varies between provinces)
  9. elective termination of pregnancy after fetal viability may be indicated under exceptional circumstances

**Ethical and Legal Concerns and Arguments**
- no law currently regulates abortion in Canada
- it is a woman’s medical decision to be made in consultation with whom she wishes; there is no mandatory role for spouse/family
- 2nd and even 3rd trimester abortions are not illegal in Canada, but are usually only carried out when there are serious risks to the woman’s health, or if the fetus has died *in utero* or has major malformations (e.g. anencephaly)

**Prenatal/Antenatal Genetic Testing**
- uses
  1. to confirm a clinical diagnosis
  2. to detect genetic predisposition to a disease
  3. allows preventative steps to be taken and helps patient prepare for the future
  4. gives parents the option to terminate a pregnancy or begin early treatment
- ethical dilemmas arise because of the sensitive nature of genetic information; important considerations of genetic testing include:
  - the individual and familial implications
  - its pertaining to future disease
  - its ability to identify disorders for which there are no effective treatments or preventive steps
  - its ability to identify the sex of the fetus
- ethical issues and arguments regarding the use of prenatal/antenatal genetic testing include:
  - obtaining informed consent is difficult due to the complexity of genetic information
  - doctor’s duty to maintain confidentiality vs. duty to warn family members
  - risk of social discrimination (e.g. insurance) and psychological harm

**Legal Aspects**
- no current specific legislation exists
- testing requires informed consent
- no standard of care exists for clinical genetics, but physicians are legally obligated to inform patients that prenatal testing exists and is available
- a physician can breach confidentiality terms in order to warn family members about a condition if harm can possibly be prevented via treatment or prevention (e.g. familial adenomatous polyposis, *Gastroenterology*, G34)

**Genetic Testing: Ethically Appropriate Actions**
- thorough discussion and realistic planning with patient before testing is done
- genetic counselling for delivery of complex information
End-of-Life Care

Overview of Palliative and End-of-Life Care
- focus of care is comfort and respect for person nearing death and maximizing quality of life for patient, family, and loved ones
- appropriate for any patient at any stage of a life-limiting illness
- may occur in a hospital, hospice, in the community, or at home
- often involves an interdisciplinary team of caregivers
- addresses the medical, psychosocial, and spiritual dimensions of care

Euthanasia and Physician-Assisted Suicide
- *euthanasia*: a deliberate act undertaken by one person with the intention of ending the life of another person to relieve that person's suffering, where the act is the cause of death
- *physician-assisted suicide*: the act of intentionally killing oneself with the assistance of a physician who deliberately provides the knowledge and/or the means

Common Ethical Arguments/Opinions
- patient has the right to make autonomous choices about the time and manner of their own death
- belief that there is no ethical difference between the acts of euthanasia/assisted suicide and foregoing life-sustaining treatments
- belief that these acts benefit terminally ill patients by relieving suffering
- patient autonomy has limits
- death should be the consequence of the morally justified withdrawal of life-sustaining treatments only in cases where there is a fatal underlying condition, and it is the condition (not the withdrawal of treatment) that causes death

Legal Aspect
- in Canada, euthanasia is a punishable offence under the Criminal Code of Canada
- in the *Carter v. Canada* decision of February 2015, physician-assisted suicide ruled to be not criminal, with the decision taking effect in 2016

Acceptable Use of Palliative and End-of-Life Care
- the use of palliative sedation with opioids in end-of-life care, knowing that death may occur as an unintended consequence (principle of double effect) is distinguished from euthanasia and assisted suicide where death is the primary intent
- the appropriate withdrawal of life-support is distinguished from euthanasia and assisted suicide as it is seen as allowing the underlying disease to take its ‘natural course’
- consent for withdrawal of life-support must be sought from SDMs, as ruled in *Cuthbertson v. Rasouli* in 2013
- refusals of care by the patient that may lead to death ought to be carefully explored by the physician to rule out any ‘reversible factors’ (e.g. poor palliation, depression, poverty, ill-education, isolation) that may be hindering authentic choice

Physician Responsibilities Regarding Death
- physicians are required by law to complete a medical certificate of death unless the coroner needs notification; failure to report death is a criminal offence
- *Coroner’s Act, 1990* (specific to Ontario, similar in other provinces) requires physicians to notify a coroner or police officer if death occurs:
  - due to violence, negligence, misconduct, misadventure, or malpractice
  - during pregnancy or is attributable to pregnancy
  - suddenly and unexpectedly
  - from disease which was not treated by a legally qualified medical practitioner
  - from any cause other than disease
  - under suspicious circumstances
- coroner investigates these deaths, as well as deaths that occur in psychiatric institutions, jails, foster homes, nursing homes, hospitals to which a person was transferred from a facility, institution or home, etc.
- in consultation with forensic pathologists and other specialists, the coroner establishes:
  - the identity of the deceased
  - where and when the death occurred
  - the medical cause of death
  - the means of death (i.e. natural, accidental, suicide, homicide, or undetermined)
- coroners do not make decisions regarding criminality or legal responsibility

Physician Competence and Professional Conduct

CanMEDS Competencies (Ethical/Policy Statement)
- a framework of professional competencies established by the MCC as objectives for the MCC Qualifying Exam
- further information on MCC objectives can be found at www.mcc.ca

Legal Considerations
- physicians' conduct and competence are legally regulated to protect patients and society via mandatory membership to provincial governing bodies (e.g., the CPSO)
- physicians are legally required to maintain a license with the appropriate authority, and are thus legally bound to outlined policies on matters of conduct within his/her medical practice

Common Policies on Physician Conduct
- physicians must ensure that patients have access to continuous on-call coverage and are never abandoned
- sexual conduct with patients, even when consented to by the patient, is a serious matter that can lead to accusations of battery by the patient and provincial governing body. Important notes on this topic include:
  - inappropriate sexual conduct includes intercourse, undue touching, references to sexual matters, sexual jokes, and physician presence when capable patients undress or dress
  - in specified situations, physicians may have a personal relationship with a patient provided a year has passed since the last therapeutic contact
  - physicians are permanently prohibited from personal relationships with patients whom they saw for psychotherapy
  - in Ontario, physicians must report any colleagues of whom they have information regarding sexual impropriety (as per CPSO Code of Ethics)
- physicians must maintain adequate records for each patient, which include:
  - demonstration that care has been continuous and comprehensive
  - minimal standards for record-keeping, including diagnosis, differential diagnosis, appropriate tests and referrals, and a coherent patient record (full standards available at www.cpsso.on.ca)
  - records stored for 10 years in most jurisdictions
  - although the medical record is the property of the physician or an institution, the patient or the patient's delegate must be allowed full access to information in the medical record upon (usually written) request
- in the hospital, physicians must ensure their own competence, respect hospital by-laws and regulations, practice only within the limits of granted privileges, cooperate with other hospital personnel, and maintain adequate hospital records

Research Ethics
- involves the systematic analysis of ethical dilemmas arising during research involving human subjects to ensure that:
  - study participants are protected
  - clinical research is conducted to serve the interests of the participants and/or society as a whole
  - major ethical dilemmas arise when a physician's obligation to the patient comes into conflict with other obligations and incentives
  - any exceptions to disclosure for therapeutic consent do not apply in an experimental situation
  - important ethical principles to consider when conducting research on human subjects were laid out in the Declaration of Helsinki, the Belmont Report, and the Tri-Council Policy Statement: Ethical Conduct on Research Involving Human Subjects
Table 5. Ethical Principles for Research Involving Human Subjects

- Patient’s participation in research should not put him/her at a known or probable disadvantage with respect to medical care (i.e. cannot deny participants in research ‘known effective care’, such as randomizing some depressed patients to a placebo arm)
- Participant’s voluntary and informed choice is usually required, except in special circumstances (i.e. chart reviews without patient contact, or emergency situations for which there is no accepted or helpful standard of care and the proposed intervention is not likely to cause more harm than such patients already face)
- Access to the treatment that is considered standard (i.e. placebo-controlled trials are generally acceptable where patients still receive the standard of care and are informed about the placebo arm and what that entails)
- Must employ a scientifically valid design to answer the research question (ensured via peer review, expert opinion)
- Must demonstrate sufficient value to justify the risk posed to participants
- Must be conducted honestly (i.e. carried out as stated in the approved protocol)
- Findings must be reported promptly and accurately without exaggeration, to allow practicing clinicians to draw reasonable conclusions
- Patients must not be enticed into risky research by the lure of money and investigators must not trade the interests of patients for disproportionate recompense by a sponsor; both participants and investigators are due fair recompense for their time and efforts
- Any significant interventional trial ought to have a data safety monitoring board that is independent of the sponsor and can ensure safety of the ongoing trial

Physician-Industry Relations

- Health care delivery in Canada involves collaboration between physicians and the pharmaceutical and health supply industries in the areas of research, education, and clinical evaluation packages (i.e. product samples)
- Physicians have a responsibility to ensure that their participation in such collaborative efforts is in keeping with their duties to their patients and society.
- Gifts or free products from the pharmaceutical industry are usually inappropriate
  - Sponsorship for travel and fees for conference attendance may be accepted only where the physician is a conference presenter and not just in attendance.
- Physicians receiving such sponsorship must disclose this at presentations and/or in written articles

Resource Allocation

- Definition: the distribution of goods and services to programs and people.
- Physicians have the duty to inform patients about therapeutic options even if they are not available.
- Physicians must make health care resources available to patients in a manner which is fair and equitable, without bias or discrimination
  - Need and benefit are morally relevant criteria for resource allocation.
  - Gender, sexual orientation, religion, level of education, or age alone are morally irrelevant criteria.
- Ethical dilemmas that arise when deciding how best to allocate resources
  - Fair chances versus best outcome: favouring best outcome vs. giving all patients fair access to limited resources (e.g. transplant list prioritization).
  - Priorities problem: how much priority should the sickest patients receive?
  - Aggregation problem: modest benefits to many vs. significant benefits to few.
  - Democracy problem: when to rely on a fair democratic process to arrive at a decision.

Guidelines for Appropriately Allocating Resources

- The physician’s primary obligation is to:
  - Protect and promote the welfare and best interests of his/her patients.
  - Choose interventions known to be beneficial on the basis of evidence of effectiveness.
  - Seek the tests or treatments that will accomplish the diagnostic or therapeutic goal for the least cost.
  - Advocate for one’s patients, but avoid manipulating the system to gain unfair advantage for them.
  - Resolve conflicting claims for scarce resources justly, on the basis of morally relevant criteria such as need and benefit, using fair and publicly defensible procedures.
  - Inform patients of the impact of cost constraints on care, but in a sensitive way.
  - Seek resolution of unacceptable shortages at the level of hospital management or government.
Conscientious Objection

Patients Refusing Treatment
- in accordance with the principle of autonomy, it is generally acceptable for competent patients to refuse medical interventions for themselves or others, although exceptions may occur
- if parents or SDMs make decisions that are clearly not in the “best interests” of an incapable child, physicians may have ethical grounds for administering treatment, depending on the acuity of the clinical situation
- in high-acuity scenarios (e.g., refusing blood transfusion based on religious grounds for a child in hemorrhagic shock), physicians have a stronger obligation to act in the child’s best interests
- in lower acuity scenarios (e.g., refusing childhood immunization in a developed nation) there is a stronger obligation to respect the autonomy of the decision-makers
- pursuing traditional First Nations healing (in conjunction or in the place of standard biomedical therapy) is legally considered a constitutionally protected right, which can be made by a SDM, as ruled in Hamilton Health Sciences v. DH in 2014

Physicians Refusing to Provide Treatment
- physicians may refuse to provide treatment or discontinue relationships with patients, but must ensure these patients can access services elsewhere (e.g. a pediatrician who refuses to treat an unvaccinated child should refer the family to another practice)

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Bioethics
Bioethics for Clinicians Series. CMAJ.


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Collier R. Steps forward no guarantee that health targets will be met, council says. CMAJ 2011;183:1919-620.


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Health Protection and Promotion Act – 1990, c. 7, O. Reg. 559/91, amended to O. Reg. 96/03.

Law


Research Ethics


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ADV assist-control ventilation
AHA American Heart Association
ALS amyotrophic lateral sclerosis
ARDS acute respiratory distress syndrome
atm atmosphere
CCS Canadian Cardiovascular Society
CK creatine kinase
CO cardiac output
CSF cerebrospinal fluid
CVP central venous pressure
DIC disseminated intravascular coagulation
ETCO₂ End-Tidal CO₂
ETT endotracheal tube
FiO₂ fraction of oxygen in inspired air
FFP fresh frozen plasma
FRF functional residual capacity
GA general anesthetic
gastroesophageal reflux disease
Hb(i) initial hematocrit
Hb(f) final hematocrit
Hct hematocrit
HES hydroxyethyl starch
ICP intracranial pressure
ICU intensive care unit
IOP intraocular pressure
LA local anesthetic
LES lower esophageal sphincter
LMA laryngeal mask airway
LOC level of consciousness
MAC minimum alveolar concentration
MAP mean arterial pressure
MH malignant hyperthermia
MS multiple sclerosis
N2O nitrous oxide
NHSA New York Heart Association
OCP operating room
PaCO₂ arterial partial pressure of carbon dioxide
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PC patient-controlled
PCMA pressure-controlled analgesia
PEEP positive end-expiratory pressure
PSAV parasympathetic nervous system
PO2 partial pressure of oxygen
PNS post-operative nausea and vomiting
PPV positive pressure ventilation
RDI rapid sequence induction
SABA short-acting β-agonist
SCh succinylcholine
SIADH syndrome of inappropriate antidiuretic hormone
SNS sympathetic nervous system
SV stroke volume
SVR systemic vascular resistance
total body water
TIVA total intravenous anesthetic
TURP transurethral resection of prostate
VO ventilation/perfusion
VT venous thromboembolism

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Overview of Anesthesia

- an anesthesia: lack of sensation/perception
- approach to anesthesia
  1. pre-operative assessment
  2. patient optimization
  3. plan anesthetic
     various types of anesthesia
     pre-medication
     airway management
     monitors
     induction
     maintenance
     extubation
  4. post-operative care

Types of Anesthesia

- general
  - general anesthesia (GA)
  - total IV anesthesia (TIVA)
- regional
  - spinal, epidural
  - peripheral nerve block
  - IV regional
- local
  - local infiltration
  - topical
- sedation
  - monitored anesthesia care
  - note that different types of anesthesia can be combined (general + regional)

General Anesthesia
- induction, maintenance and extubation

Pre-Operative Assessment

Purpose
- identify patient's medical and surgical issues
- allow for questions to help allay any fears or concerns patient and/or family may have
- arrange further investigations, consultations and treatments for patients not yet optimized
- plan and consent for anesthetic techniques

History and Physical

History
- age, gender
- indication for surgery
- surgical/anesthetic Hx: previous anesthetics, any complications, previous intubations, medications, drug allergies, post-operative N/V
- FHx: abnormal anesthetic reactions, malignant hyperthermia, pseudocholinesterase deficiency (see Uncommon Complications, A26)
- PMHx
  - CNS: seizures, TIA/strokes, raised ICP, spinal disease, aneurysm
  - CVS: angina/CAD, MI, CHF, HTN, valvular disease, dysrhythmias, peripheral vascular disease (PVD), conditions requiring endocarditis prophylaxis, exercise tolerance, CCS/NYHA class (Cardiology and Cardiac Surgery, C37 for NYHA classification)
  - respiratory: smoking, asthma, COPD, recent upper respiratory tract infection, sleep apnea
  - GI: GERD, liver disease, NPO status
  - renal: insufficiency, dialysis, chronic kidney disease
  - hematologic: anemia, coagulopathies, blood dyscrasias
  - MSK: conditions associated with difficult intubations – arthritides (e.g. rheumatoid arthritis), cervical tumours, cervical infections/abscesses, trauma to cervical spine, previous cervical spine surgery, Trisomy 21, scleroderma, conditions affecting neuromuscular junction (e.g. myasthenia gravis)
  - endocrine: DM, thyroid disorders, adrenal disorders
  - other: morbid obesity, pregnancy, ethanol/other drug use

Physical Exam
- weight, height, BP, pulse, respiratory rate, oxygen saturation
- general assessment of nutrition, hydration and mental status
- focused physical exam of the CNS, CVS, and respiratory systems
- general assessment of nutrition, hydration, and mental status
• airway assessment
  - done to determine intubation difficulty (no single test is specific or sensitive)
  - cervical spine stability and neck movement – upper cervical spine extension, lower cervical spine flexion (“sniffing position”)
  - Mallampati classification
  - “3-2-1 rule”
    - thyromental distance (distance of lower mandible in midline from the mentum to the thyroid notch); <3 finger breadths (<6 cm) is associated with difficult intubation
    - mouth opening (<2 finger breadths is associated with difficult intubation)
    - anterior jaw subluxation (<1 finger breadth is associated with difficult intubation)
  - tongue size
  - dentition, dental appliances/prosthetic caps, existing chipped/loose teeth – must inform patients of rare possibility of damage
  - nasal passage patency (if planning nasotracheal intubation)
  - assess difficulty of ventilation
• examination of anatomical sites relevant to lines and blocks
  - bony landmarks and suitability of anatomy for regional anesthesia (if relevant)
  - sites for IV, central venous pressure (CVP), and pulmonary artery (PA) catheters

Table 1. Suggested Indications for Specific Investigations in the Pre-Operative Period

<table>
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<tr>
<th>Test</th>
<th>Indications</th>
</tr>
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<td>Major surgery requiring group and screen or cross and match; chronic cardiovascular, pulmonary, renal, or hepatic disease; malignancy; known or suspected anemia; bleeding diathesis or myelosuppression; patient less than 1 yr</td>
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<td>Sickle Cell Screen</td>
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Figure 1. Mallampati classification of oral opening

Pre-Operative Investigations

• routine pre-operative investigations are only necessary if there are comorbidities or certain indications

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American Society of Anesthesiology Classification

- common classification of physical status at the time of surgery
- a gross predictor of overall outcome, NOT used as stratification for anesthetic risk (mortality rates)
- ASA 1: a healthy, fit patient
- ASA 2: a patient with mild systemic disease
  - e.g. controlled Type 2 DM, controlled essential HTN, obesity, smoker
- ASA 3: a patient with severe systemic disease that limits activity
  - e.g. stable CAD, COPD, DM, obesity
- ASA 4: a patient with incapacitating disease that is a constant threat to life
  - e.g. unstable CAD, renal failure, acute respiratory failure
- ASA 5: a moribund patient not expected to survive 24 h without surgery
  - e.g. ruptured abdominal aortic aneurysm (AAA), head trauma with increased ICP
- ASA 6: declared brain dead, a patient whose organs are being removed for donation purposes
- for emergency operations, add the letter E after classification (e.g. ASA 3E)

Pre-Operative Optimization

- in general, prior to elective surgery
  - any fluid and/or electrolyte imbalance should be corrected
  - extent of existing comorbidities should be understood and these conditions should be optimized prior to surgery
  - medications may need to be adjusted

Medications

- pay particular attention to cardiac and respiratory medications, opioids and drugs with many side effects and interactions
- **pre-operative medications to consider**
  - prophylaxis
    - risk of GE reflux: sodium citrate 30 mL PO and/or ranitidine 150-300 mg PO and/or metoclopramide 10 mg PO 30 min-1 h prior to surgery
    - risk of infective endocarditis, GI/GU interventions: antibiotics
    - risk of adrenal suppression: steroid coverage
    - anxiety: consider benzodiazepines
    - COPD, asthma: bronchodilators
    - CAD risk factors: nitroglycerin and β-blockers
- **pre-operative medications to stop**
  - oral antihyperglycemics: stop on morning of surgery
  - antidepressants: stop on morning of surgery
  - ACE inhibitors and angiotension receptor blockers: may stop on morning of surgery (controversial)
  - warfarin (consider bridging with heparin), anti-platelet agents (e.g. clopidogrel)
    - discuss perioperative use of ASA, NSAIDs with surgeon
  - in patients undergoing non-cardiac surgery, starting or continuing low-dose aspirin in the perioperative period does not appear to protect against post-operative MI or death, but increases the risk of major bleeding
    - note: this does not apply to patients with bare metal stents or drug-eluting coronary stents
- **pre-operative medications to adjust**
  - insulin (consider insulin/dextrose infusion or holding dose), prednisone, bronchodilators

Hypertension

- BP <180/110 is not an independent risk factor for perioperative cardiovascular complications
- target sBP <180 mmHg, dBP <110 mmHg
- assess for end-organ damage and treat accordingly
**Coronary Artery Disease**

- ACC/AHA Guidelines (2014) recommend that at least 60 days should elapse after a MI before a noncardiac surgery in the absence of a coronary intervention
  - this period carries an increased risk of reinfarction/death
- if operative procedure is essential and cannot be delayed, invasive intra- and post-operative ICU monitoring is needed
- mortality with perioperative MI is 20-50%
- peroperative β-blockers
  - may ↓ cardiac events and mortality (controversial, as recent data suggests ↑ stroke risk)
  - continue β-blocker if patient is routinely taking it prior to surgery
  - consider initiation of β-blocker in
    - patients with CAD or indication for β-blocker
    - intermediate risk surgery, especially vascular surgery

**Respiratory Diseases**

- smoking
  - adverse effects: altered mucus secretion and clearance, decreased small airway caliber, and altered immune response
  - abtain at least 8 wk pre-operatively if possible
  - if unable, abstaining even 24 h pre-operatively has shown benefit
- asthma
  - pre-operative management depends on degree of baseline asthma control
  - increased risk of bronchospasm from intubation, delivery of desflurane
    - administration of short course (up to 1 wk) pre-operative corticosteroids and inhaled β2-agonists decreases the risk of bronchospasm and does not increase the risk of infection or delay wound healing
  - avoid non-selective β-blockers due to risk of bronchospasm
  - cardioselective β-blockers (metoprolol, atenolol) do not increase risk of bronchospasm in the short-term
  - delay elective surgery for poorly controlled asthma (increased cough or sputum production, active wheezing)
  - delay elective surgery by a minimum of 6 wk if patient develops URTI
- COPD
  - anesthesia, surgery (especially abdominal surgery, in particular upper abdominal surgery) and pain predispose the patient to atelectasis, bronchospasm, pneumonia, prolonged need for mechanical ventilation, and respiratory failure
  - pre-operative ABG for all COPD stage II and III patients to assess baseline respiratory acidosis and plan post-operative management of hypercapne
  - cancel/delay elective surgery for acute exacerbation

**Aspiration**

- increased risk of aspiration with
  - decreased LOC
  - trauma
  - meals within 8 h
  - suspected sphincter incompetence (GERD, hiatus hernia, nasogastric tube)
  - increased abdominal pressure (pregnancy, obesity, bowel obstruction, acute abdomen)
  - laryngeal mask vs. endotracheal tube (ETT)
- management
  - reduce gastric volume and acidity
  - delay inhibiting airway reflexes with muscular relaxants
  - employ rapid sequence induction (see Rapid Sequence Induction, A16)

**Fasting Guidelines**

**Fasting Guidelines Prior to Surgery (Canadian Anesthesiologists’ Society)**

- 8 h after a meal that includes meat, fried or fatty foods
- 6 h after a light meal (such as toast or crackers) or after ingestion of infant formula or non-human milk
- 4 h after ingestion of breast milk
- 2 h after clear fluids (water, black coffee, tea, carbonated beverages, juice without pulp)
Hematological Disorders

- history of congenital or acquired conditions (sickle cell anemia, factor VIII deficiency, ITP, liver disease)
- evaluate hemoglobin, hematocrit and coagulation profiles when indicated (Table 1)
- anemia
  - pre-operative treatments to increase hemoglobin (erythropoietin or pre-admission blood collection in certain populations)
- coagulopathies
  - discontinue or modify anticoagulation therapies (warfarin, clopidogrel, ASA) in advance of elective surgeries
  - administration of reversal agents if necessary: vitamin K, FFP, prothrombin complex concentrate, recombinant activated factor VII

Endocrine Disorders

- diabetes mellitus
  - clarify type 1 vs. type 2
  - clarify treatment – oral antihyperglycemics and/or insulin
  - assess glucose control with history and HbA1c; well controlled diabetics have more stable glucose levels intraoperatively
  - end organ damage: be aware of damage to CVS, renal, and nervous systems, including autonomic neuropathy
  - formulate intraoperative glucose management plan based on type (1 vs. 2), glucose control, and extent of end organ damage
- hyperthyroidism
  - can experience sudden release of thyroid hormone (thyroid storm) if not treated or well-controlled preoperatively
  - treatment: β-blocking agents and pre-operative prophylaxis
- adrenocortical insufficiency (Addison's, exogenous steroid use)
  - consider intraoperative steroid supplementation

Obesity and Obstructive Sleep Apnea

- assess for comorbid conditions in obese patient (independent risk factor for CVD, DM, OSA, cholelithiasis, HTN)
- previously undiagnosed conditions may require additional testing to characterize severity
- both obesity and OSA increase risk of difficult ventilation, intubation and post-operative respiratory complications
  - risk may be magnified with both diseases present

Monitoring

Canadian Guidelines to the Practice of Anesthesia and Patient Monitoring

- an anesthetist present: "the only indispensable monitor"
- a completed pre-anesthetic checklist: including ASA class, NPO policy, Hx and investigations
- a perioperative anesthetic record: HR and BP every 5 min, dose and route of drugs and fluids
- continuous monitoring: see Routine Monitors for All Cases

Routine Monitors for All Cases

- pulse oximeter, apparatus to measure BP, electrocardiography and capnography are required for general anesthesia and sedation (Ramsey Sedation Scale 4-6), agent-specific anesthetic gas monitor when inhalational anesthetic agents are used
- the following must also be available: temperature probe, peripheral nerve stimulator, stethoscope, appropriate lighting, spirometer

Elements to Monitor

- anesthetic depth
  - inadequate: blink reflex present when eyelashes lightly touched, HTN, tachycardia, tearing or sweating
  - excessive: hypotension, bradycardia
- oxygenation: pulse oximetry, fraction of inspired O₂ (FiO₂)
- ventilation: verify correct position of ETT, chest excursions, breath sounds, ET₃₀₂ analysis, end tidal inhaled anesthesia analysis
- circulation: pulse, heart sounds, BP, telemetry, oximetry, CVP, pulmonary capillary wedge pressure
- temperature
Airway Management

**Airway Anatomy**

- resistance to airflow through nasal passages accounts for approximately 2/3 of total airway resistance
- pharyngeal airway extends from posterior aspect of the nose to cricoid cartilage
- glottic opening (triangular space formed between the true vocal cords) is the narrowest segment of the laryngeal opening in adults
- the glottic opening is the space through which one visualizes proper placement of the ETT
- the trachea begins at the level of the thyroid cartilage, C6, and bifurcates into the right and left main bronchi at T4-T5 (approximately the sternal angle)

**Methods of Supporting Airways**

1. non-definitive airway (patent airway)
   - jaw thrust/chin lift
   - oropharyngeal and nasopharyngeal airway
   - bag mask ventilation
   - laryngeal mask airway
2. definitive airway (patent and protected airway)
   - endotracheal tube
   - surgical airway (cricothyrotomy or tracheostomy)

**Table 2. Methods of Supporting the Airway**

<table>
<thead>
<tr>
<th>Bag and Mask</th>
<th>Laryngeal Mask Airway (LMA)</th>
<th>Endotracheal Tube (ETT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advantages/Indications</td>
<td>Easy to insert</td>
<td>Indications for intubation (5 Ps)</td>
</tr>
<tr>
<td></td>
<td>Less airway trauma/irritation than ETT</td>
<td>Patent airway</td>
</tr>
<tr>
<td></td>
<td>Frees up hands (vs. face mask)</td>
<td>Protects against aspiration</td>
</tr>
<tr>
<td></td>
<td>Primarily used in spontaneously ventilating patient</td>
<td>Positive pressure ventilation</td>
</tr>
<tr>
<td>Disadvantages/Contraindications</td>
<td>Risk of aspiration if decreased LOC</td>
<td>Insertion can be difficult</td>
</tr>
<tr>
<td></td>
<td>Cannot ensure airway patency</td>
<td>Muscle relaxant usually needed</td>
</tr>
<tr>
<td></td>
<td>Inability to deliver precise tidal volume</td>
<td>Most invasive – see Complications During Laryngoscopy and Intubation, A9</td>
</tr>
<tr>
<td></td>
<td>Operator fatigue</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Sizing by body weight (approx)</td>
<td>Auscultate to avoid endobronchial intubation</td>
</tr>
<tr>
<td></td>
<td>40-50 kg: 3</td>
<td>Sizing (approx):</td>
</tr>
<tr>
<td></td>
<td>50-70 kg: 4</td>
<td>Male: 6.0-9.0 mm</td>
</tr>
<tr>
<td></td>
<td>70-100 kg: 5</td>
<td>Female: 7.0-8.0 mm</td>
</tr>
<tr>
<td></td>
<td>Can use oropharyngeal/nasopharyngeal airway</td>
<td>Pediatric: (age/4) + 4 mm</td>
</tr>
</tbody>
</table>
Tracheal Intubation

Preparing for Intubation
- failed attempts at intubation can make further attempts more difficult due to tissue trauma
- plan, prepare, and assess for potential difficulties (see Pre-Operative Assessment, A2)
- ensure equipment is available and working (test ETT cuff, check laryngoscope light and suction, machine check)
- pre-oxygenate/denitrogenate: patient breathes 100% O₂ for 3-5 min or for 4 vital capacity breaths
- may need to suction mouth and pharynx first

Proper Positioning for Intubation
- align the three axes (mouth, pharynx, and larynx) to allow visualization from oral cavity to glottis
  - “snifﬁng position”: ﬂexion of lower C-spine (C5-C6), bow head forward, and extension of upper C-spine at atlanto-occipital joint (C1), nose in the air
  - contraindicated in known/suspected C-spine fracture/instability
- laryngoscope tip placed in the epiglottic vallecula in order to visualize cord

Tube Insertion
- laryngoscopy and ETT insertion can incite a signiﬁcant sympathetic response via stimulation of cranial nerves 9 and 10 due to a “foreign body reﬂex” in the trachea, including tachycardia, dysrhythmias, myocardial ischemia, increased BP, and coughing
- a malpositioned ETT is a potential hazard for the intubated patient
  - if too deep, may result in right endobronchial intubation, which is associated with left-sided atelectasis and right-sided tension pneumothorax
  - if too shallow, may lead to accidental extubation, vocal cord trauma, or laryngeal paralysis as a result of pressure injury by the ETT cuff
- the tip of ETT should be located at the midpoint of the trachea at least 2 cm above the carina and the proximal end of the cuff should be placed at least 2 cm below the vocal cords
  - approximately 20-23 cm mark at the right corner of the mouth for men and 19-21 cm for women
Confirmation of Tracheal Placement of ETT
- direct
  - visualization of ETT passing through cords
  - bronchoscopic visualization of ETT in trachea
- indirect
  - \(\text{ETCO}_2\) in exhaled gas measured by capnography
  - auscultate for equal breath sounds bilaterally and absent breath sounds over epigastrium
  - bilateral chest movement, condensation of water vapour in ETT visible during exhalation and no abdominal distention
  - filling of reservoir bag during exhalation
  - CXR (rarely done): only confirms position of the tip of ETT and not that ETT is in the trachea
- esophageal intubation suspected when
  - \(\text{ETCO}_2\) zero or near zero on capnograph
  - abnormal sounds during assisted ventilation
  - impairment of chest excursion
  - hypoxia/cyanosis
  - presence of gastric contents in ETT
  - distention of stomach/epigastrium with ventilation

Complications During Laryngoscopy and Intubation
- dental damage
- laceration (lips, gums, tongue, pharynx, esophagus)
- laryngeal trauma
- esophageal or endobronchial intubation
- accidental extubation
- insufficient cuff inflation or cuff laceration: results in leaking and aspiration
- laryngospasm (see Extubation, A18 for definition)
- bronchospasm

Difficult Airway
- difficulties with bag-mask ventilation, supraglottic airway, laryngoscopy, passage of ETT through the cords, infraglottic airway or surgical airway
- algorithms exist for difficult airways (Can J Anesth 2013;60:1119-1138; Anesthesiology 2003;98:3273; Anesthesiology 2013;118:251-270), see Figures 14 and 15, A30, A31
- pre-operative assessment (history of previous difficulties, airway examination) and pre-operative assessment (history of previous intubation history)
- if difficult airway expected, consider
  - awake intubation
  - intubating with bronchoscope, trachlight (lighted stylet), fibre optic laryngoscope, glidescope, etc.
- if intubation unsuccessful after induction
  1. CALL FOR HELP
  2. ventilate with 100% \(O_2\) via bag and mask
  3. consider returning to spontaneous ventilation and/or waking patient
- if bag and mask ventilation inadequate
  1. CALL FOR HELP
  2. attempt ventilation with oral airway
  3. consider/attempt LMA
  4. emergency invasive airway access (e.g. rigid bronchoscope, cricothyrotomy, or tracheostomy)

Oxygen Therapy
- in general, the goal of oxygen therapy is to maintain arterial oxygen saturation (\(\text{SaO}_2\)) >90%
- small decrease in saturation below \(\text{SaO}_2\) of 90% corresponds to a large drop in arterial partial pressure of oxygen (\(\text{PaO}_2\))
- in intubated patients, oxygen is delivered via the ETT
- in patients not intubated, there are many oxygen delivery systems available; the choice depends on oxygen requirements (\(\text{FiO}_2\)) and the degree to which precise control of delivery is needed
- cyanosis can be detected at \(\text{SaO}_2\) <85%, frank cyanosis at \(\text{SaO}_2\) = 67%

Low Flow Systems
- acceptable if tidal volume 300-700 mL, respiratory rate (RR) <25, consistent ventilation pattern
- provide \(O_2\) at flows between 0-10 L/min
- dilution of oxygen with room air results in a decrease in \(\text{FiO}_2\)
- an increase in minute ventilation (tidal volume x RR) results in a decrease in \(\text{FiO}_2\)
  - e.g. nasal canula (prong)
Reservoir Systems
- use a volume reservoir to accumulate oxygen during exhalation thus increasing the amount of oxygen available for the next breath
- simple face mask
  - covers patient's nose and mouth and provides an additional reservoir beyond nasopharynx
  - fed by small bore O₂ tubing at a rate of at least 6 L/min to ensure that exhaled CO₂ is flushed through the exhalation ports and not rebreathed
  - provides FiO₂ of 55% at O₂ flow rates of 10 L/min
- non-rebreather mask
  - a reservoir bag and a series of one-way valves prevent expired gases from re-entering the bag during the exhalation phase, the bag accumulates with oxygen
  - provides FiO₂ of 80% at O₂ flow rates of 10-15 L/min

High Flow Systems
- generate flows of up to 50-60 L/min
- meet/exceed patient's inspiratory flow requirement
- deliver consistent and predictable concentration of O₂
- Venturi mask
  - delivers specific FiO₂ by varying the size of air entrapment
  - oxygen concentration determined by mask's port and NOT the wall flow rate
  - enables control of gas humidity
  - FiO₂ ranges from 24-50%

Ventilation
- ventilation is maintained with PPV in patients given muscle relaxants
- assisted or controlled ventilation can also be used to assist spontaneous respirations in patients not given muscle relaxants as an artificial means of supporting ventilation and oxygenation

Mechanical Ventilation
- indications for mechanical ventilation
  - apnea
  - hypoventilation/acute respiratory acidosis
  - intraoperative positioning limiting respiratory excursion (e.g. prone, Trendelenburg)
  - required hyperventilation (to lower ICP)
  - deliver positive end expiratory pressure (PEEP)
  - increased intrathoracic pressure (e.g. laparoscopic procedure)
- complications of mechanical ventilation
  - airway complications
    - tracheal stenosis, laryngeal edema
    - alveolar complications
    - ventilator-induced lung injury, ventilator-associated pneumonia (nosocomial pneumonia), barotrauma, volutrauma, inflammation, auto-PEEP, patient-ventilator asynchrony
  - cardiovascular complications
    - reduced venous return (secondary to increased intrathoracic pressure), reduced cardiac output, hypotension
    - neuromuscular complications
    - muscle atrophy
    - increased intracranial pressure
    - metabolic
      - decreased CO₂ due to hyperventilation
      - alkalemia with over correction of chronic hypercarbia

Ventilator Strategies
- mode and settings are determined based on patient factors (e.g. ideal body weight, compliance, resistance) and underlying reason for mechanical ventilation
- hypoxemic respiratory failure: ventilator provides supplemental oxygen, recruits atelectatic lung segments, helps improve V/Q mismatch, and decreases intrapulmonary shunt
- hypercapnic respiratory failure: ventilator augments alveolar ventilation; may decrease the work of breathing, allowing respiratory muscles to rest

Composition of Air
- 78.1% nitrogen
- 20.9% oxygen
- 0.9% argon
- 0.04% carbon dioxide

Changes in peak pressures in ACV and tidal volumes in PCV may reflect changes in lung compliance and/or airway resistance – patient may be getting better or worse

Positive End Expiratory Pressure (PEEP)
- Positive pressure applied at the end of ventilation that helps to keep alveoli open, decreasing V/Q mismatch
- Used with all invasive modes of ventilation

Tracheostomy
- Tracheostomy should be considered in patients who require ventilator support for extended periods of time
- Shown to improve patient comfort and give patients a better ability to participate in rehabilitation activities

Monitoring Ventilatory Therapy
- Pulse oximetry, end-tidal CO₂ concentration
- Regular arterial blood gases
- Assess tolerance regularly

Management of pneumothorax in patients on mechanical ventilation → chest tube
Modes of Ventilation

- assist control ventilation (ACV) or volume control
  - every breath is delivered with a pre-set tidal volume and rate or minute ventilation
  - extra controlled breaths may be triggered by patient effort; if no effort is detected within a specified amount of time the ventilator will initiate the breath
- pressure control ventilation (PCV)
  - a minimum frequency is set and patient may trigger additional breaths above the ventilator
  - all breaths delivered at a preset constant inspiratory pressure
- synchronous intermittent mandatory ventilation (SIMV)
  - ventilator provides controlled breaths (either at a set volume or pressure)
  - patient can breathe spontaneously (these breaths may be pressure supported) between controlled breaths
- pressure support ventilation (PSV)
  - patient initiates all breaths and the ventilator supports each breath with a pre-set inspiratory pressure
  - useful for weaning off ventilator
- high-frequency oscillatory ventilation (HFOV)
  - high breathing rate (up to 900 breaths/min in an adult), very low tidal volumes
  - used commonly in neonatal and pediatric respiratory failure
  - used in adults when conventional mechanical ventilation is failing
- non-invasive positive pressure ventilation (NPPV)
  - achieved without intubation by using a nasal or face mask
    - BiPAP: increased pressure (like PSV) on inspiration and lower constant pressure on expiration
    - CPAP: delivers constant pressure on both inspiration and expiration

### Table 3. Causes of Abnormal End Tidal CO₂ Levels

<table>
<thead>
<tr>
<th>Hypocapnea (Decreased CO₂)</th>
<th>Hypercapnea (Increased CO₂)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperventilation</td>
<td>Hypoventilation</td>
</tr>
<tr>
<td>Hypothermia (decreased metabolic rate)</td>
<td>Hyperthermia and other hypermetabolic states</td>
</tr>
<tr>
<td>Decreased pulmonary blood flow (decreased cardiac output)</td>
<td>Improved pulmonary blood flow after resuscitation or hypotension</td>
</tr>
</tbody>
</table>

- Technical issues
- Incorrect placement of sampling catheter
- Inadequate sampling volume

- V/Q mismatch
  - Pulmonary thromboembolism
  - Incipient pulmonary edema
  - Air embolism

- Low bicarbonate

Intraoperative Management

**Temperature**

**Causes of Hypothermia (<36.0°C)**

- intraoperative temperature losses are common (e.g. 90% of intraoperative heat loss is transcutaneous), due to
  - OR environment (cold room, IV fluids, instruments)
  - open wound
  - prevent with inflated warming blanket and warmed IV fluids

**Causes of Hyperthermia (>37.5-38.3°C)**

- drugs (e.g. atropine)
- blood transfusion reaction
- infection/sepsis
- medical disorder (e.g. thyrotoxicosis)
- malignant hyperthermia (see Uncommon Complications, A26)
- over-zealous warming efforts
Heart Rate

Intraoperative Tachycardia
- tachycardia = HR >150 bpm; divided into narrow complex supraventricular tachycardias (SVT) or wide complex tachycardias
- SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
- wide complex tachycardia: VT, SVT with aberrant conduction
- causes of sinus tachycardia
  - shock/hypovolemia/blood loss
  - anxiety/pain/light anesthesia
  - full bladder
  - anemia
  - febrile illness/sepsis
  - drugs (e.g. atropine, cocaine, dopamine, epinephrine, ephedrine, isoflurane, isoproterenol, pancuronium)
- Addisonian crisis, hypoglycemia, transfusion reaction, malignant hyperthermia
- for management of tachycardia, see ACLS Guidelines (Figure 17), A33

Intraoperative Bradycardia
- bradycardia = HR <50 bpm; most concerning are 2nd degree (Type 2 Mobitz) and 3rd degree heart block, which can both degenerate into asystole
- causes of sinus bradycardia
  - increased parasympathetic tone vs. decreased sympathetic tone
  - must rule out hypoxemia
  - arrhythmias (see Cardiology and Cardiac Surgery, C17)
  - baroreceptor reflex due to increased ICP or increased BP
  - vagal reflex (ocularcardiac reflex, carotid sinus reflex, airway manipulation)
  - drugs (e.g. Sch, opioids, edrophonium, neostigmine, halothane, digoxin, β-blockers)
  - high spinal/epidural anesthesia
- for management of bradycardia, see ACLS Guidelines (Figure 18), A33

Cardiac Arrest
- pulseless arrest occurs due to 4 cardiac rhythms divided into shockable and non-shockable rhythms
  - shockable: ventricular fibrillation (VF) and ventricular tachycardia (VT)
  - non-shockable: asystole and pulseless electrical activity (PEA)
- for VF/VT, key to survival is good early CPR and defibrillation
- for asystole/PEA, key to survival is good early CPR and exclude all reversible causes
- reversible causes of PEA arrest (5 Hs and 5 Ts)
  - 5 Hs: hypothermia, hypovolemia, hypoxia, hydrogen ions (acidosis), hypo/hyperkalemia
  - 5 Ts: tamponade (cardiac), thrombosis (pulmonary), thrombosis (coronary), tension pneumothorax, toxins (overdose/poisoning)
- for management of cardiac arrest, see ACLS Guidelines (Figure 16), A32

Blood Pressure

Causes of Intraoperative Hypotension/Shock
- shock: condition characterized by inability of cardiovascular system to maintain adequate end-organ perfusion and delivery of oxygen to tissues
a) hypovolemic/hemorrhagic shock
  - most common form of shock, due to decrease in intravascular volume
b) obstructive shock
  - obstruction of blood into or out of the heart
  - increased JVP, distended neck veins, increased systemic vascular resistance, insufficient cardiac output (CO)
  - e.g. tension pneumothorax, cardiac tamponade, pulmonary embolism
c) cardiogenic shock
  - myocardial dysfunction
  - SVT: sinus tachycardia, atrial fibrillation/flutter, accessory pathway mediated tachycardia, paroxysmal atrial tachycardia
  - increased JVP, distended neck veins, increased systemic vascular resistance, decreased CO
  - e.g. dysrhythmias, ischemia/infarct, cardiomyopathy, acute valvular dysfunction
d) septic shock
  - see Infectious Diseases, ID21
  - bacterial, viral, fungal, endotoxins/mediators cause vasodilation and capillary leakage
  - associated with contamination of open wounds, intestinal injury or penetrating trauma
  - signs: fever, decreased JVP, wide pulse pressure, increased CO, increased HR, decreased systemic vascular resistance ± pressors
  - initial treatment: antibiotics, volume expansion, vasopressors

BP = CO x SVR, where CO = SV x HR
SV is a function of preload, afterload, and contractility
c) spinal/neurogenic shock
   - decreased sympathetic tone
   - hypotension without tachycardia or peripheral vasoconstriction (warm skin)
f) anaphylactic shock
   - see Emergency Medicine, ER29
   - acute/subacute generalized allergic reaction due to an inappropriate or excessive immune response (type I hypersensitivity)
   - treatment of anaphylactic shock
     - moderate reaction: generalized urticaria, angioedema, wheezing, tachycardia
       - epinephrine (1:1000) 0.3-0.5 mg IM
       - antihistamines: diphenhydramine (Benadryl®) 25-50 mg IM
       - salbutamol (Ventolin®) 1 cc via MDI
     - severe reaction/evolution: severe wheezing, laryngeal/pulmonary edema, shock
       - ABCs, may need ETT due to airway edema
       - epinephrine (1:1000) 0.1-0.3 mg IV (or via ETT if no IV access) to start, repeat as needed
       - antihistamines: diphenhydramine (Benadryl®) 50 mg IV (~1 mg/kg)
       - steroids: hydrocortisone (Solucortef®) 100 mg IV (~1.5 mg/kg) or methylprednisolone (Solumedrol®) 1 mg/kg IV q6h x 24 h
       - large volumes of crystalloid may be required
g) drugs
   - vasodilators, high spinal anesthetic interfering with sympathetic outflow
h) other
   - transfusion reaction, Addisonian crisis, thyrotoxicosis, hypothyroid, aortocaval syndrome
   - see Hematology, H54 and Endocrinology, E34, E22, E26

Causes of Intraoperative Hypertension
- inadequate anesthesia causing pain and anxiety
- pre-existing HTN, coarctation, or preeclampsia
- hypoxemia/hypercarbia
- hypervolemia
- increased intracranial pressure
- full bladder
- drugs (e.g. ephedrine, epinephrine, cocaine, phenylephrine, ketamine)
- allergic/anaphylactic reaction
- hypermetabolic states: malignant hyperthermia, neuroleptic malignant syndrome, serotonin syndrome (see Psychiatry, PS46), thyroid storm, pheochromocytoma (see Endocrinology, E25, E35)

Fluid Balance and Resuscitation
- total requirement = maintenance + deficit + ongoing loss
- in surgical settings this formula must take into account multiple factors including pre-operative fasting/decreased fluid intake, increased losses during or before surgery, fluid shifting during surgery, fluids given with blood products and medications

What is the Maintenance?
- average healthy adult requires approximately 2500 mL water/d
  - 200 mL/d GI losses
  - 800 mL/d insensible losses (respiration, perspiration)
  - 1500 mL/d urine (be aware of renal failure)
- 4:2:1 rule to calculate maintenance requirements (applies to crystalloids only)
  - 4 mL/kg/h first 10 kg
  - 2 mL/kg/h second 10 kg
  - 1 mL/kg/h for remaining weight >20 kg
- increased requirements with fever, sweating, GI losses (vomiting, diarrhea, NG suction), adrenal insufficiency, hyperventilation, and polyuric renal disease
- decreased requirements with anuria/oliguria, SIADH, highly humidified atmospheres, and CHF
- maintenance electrolytes
  - Na⁺: 3 mEq/kg/d
  - K⁺: 1 mEq/kg/d
- 50 kg patient maintenance requirements
  - fluid = 40 + 20 + 30 = 90 mL/h = 2160 mL/d = 2.16 L/d
  - Na⁺ = 150 mEq/d (therefore 150 mEq / 2.16 L/d = 69 mEq/L)
  - K⁺ = 50 mEq/d (therefore 50 mEq / 2.16 L/d = 23 mEq/L)
- above patient's requirements roughly met with 2/3 D5W, 1/3 NS
  - 2/3 + 1/3 at 100 mL/h with 20 mEq KCl per litre
What is the Deficit?

- patients should be adequately hydrated prior to anesthesia
- total body water (TBW) = 60% or 50% of total body weight for an adult male or female, respectively (e.g. for a 70 kg adult male TBW = 70 x 0.6 = 42 L)
- total Na⁺ content determines ECF volume; [Na⁺] determines ICF volume
- hypovolemia due to volume contraction
  - extra-renal Na⁺ loss
    - GI: vomiting, NG suction, drainage, fistulae, diarrhea
    - skin/resp: insensible losses (fever), sweating, burns
    - vascular: hemorrhage
  - renal Na⁺ and H₂O loss
    - diuretics
    - osmotic diuresis
    - hypoadosteronism
    - salt-wasting nephropathies
  - renal H₂O loss
    - diabetes insipidus (central or nephrogenic)
  - hypovolemia with normal or expanded ECF volume
  - decreased CO
  - redistribution
    - hypoalbuminemia: cirrhosis, nephrotic syndrome
    - capillary leakage: acute pancreatitis, rhabdomyolysis, ischemic bowel, sepsis, anaphylaxis
- replace water and electrolytes as determined by patient’s needs
- with chronic hyponatremia, correction must be done gradually over >48 h to avoid central pontine myelinolysis

Table 4. Signs and Symptoms of Dehydration

<table>
<thead>
<tr>
<th>Percentage of Body Water Loss</th>
<th>Severity</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>3%</td>
<td>Mild</td>
<td>Decreased skin turgor, sunken eyes, dry mucous membranes, dry tongue, reduced sweating</td>
</tr>
<tr>
<td>6%</td>
<td>Moderate</td>
<td>Oliguria, orthostatic hypotension, tachycardia, low volume pulse, cool extremities, reduced filling of peripheral veins and CVP, hemococoncentration, apathy</td>
</tr>
<tr>
<td>9%</td>
<td>Severe</td>
<td>Profound oliguria or anuria and compromised CNS function with or without altered sensorium</td>
</tr>
</tbody>
</table>

What are the Ongoing Losses?

- losses from Foley catheter, NG, surgical drains
- third-spacing (other than ECF, ICF)
  - pleura, GI, retroperitoneal, peritoneal
  - evaporation via exposed viscera, burns
- blood loss
- ongoing loss due to surgical exposure and evaporative losses

IV Fluids

- replacement fluids include crystalloid and colloid solutions
- IV fluids improve perfusion but NOT O₂ carrying capacity of blood

Initial Distribution of IV Fluids

- H₂O follows ions/molecules to their respective compartments

Crystalloid Infusion

- salt-containing solutions that distribute only within ECF
- maintain euvolemia in patient with blood loss: 3 mL crystalloid infusion per 1 mL of blood loss for volume replacement (i.e. 3:1 replacement)
- if large volumes are to be given, use balanced fluids such as Ringer’s lactate or Plasmalyte®, as too much normal saline (NS) may lead to hyperchloremic metabolic acidosis

Colloid Infusion (see Blood Products, A15)

- includes protein colloids (albumin and gelatin solutions) and non-protein colloids (dextrans and starches e.g. hydroxyethyl starch [HES])
- distributes within intravascular volume
- 1:1 ratio (infusion:blood loss) only in terms of replacing intravascular volume
- HES colloids remain in intravascular space (metabolized by plasma serum amylase and renally excreted); two available in Canada: Voluven® and Pentaspan®

Colloids vs. Crystalloids for Fluid Resuscitation in Critically Ill Patients

Cochrane Database System Rev 2012;6:CD000567

Purpose: To evaluate the effects of colloids compared to crystalloids for fluid resuscitation, specifically when used in critically ill patients.

Methods: A meta-analysis was performed looking at randomized controlled trials comparing colloid vs. crystalloid use in patients requiring volume replacement. Pregnant women and neonates were excluded. Primary outcome was overall mortality.

Results: Results were broken down based on specific colloid. For albumin (or plasma protein fraction) the relative risk (RR) was 1.01 (95% CI 0.93-1.10) as compared to crystalloid. For hydroxyethyl starch the RR was 1.10 (95% CI 0.91-1.32). Modified gelatin had a RR of 0.91 (95% CI 0.49-1.72) and Dextran had a RR of 1.24 (95% CI 0.94-1.65). For colloids mixed in a hypertonic crystalloid as compared to isotonic crystalloid the RR was 0.88 (95% CI 0.71-1.08).

Conclusions: There is no evidence that use of colloids improves survival in trauma patients, burn patients, or post-operative patients when compared to crystalloid solutions. Given the increased cost of colloids as compared to crystalloids, it is recommended that crystalloids be the fluid of choice in these patients.
• the use of HES solutions is controversial because of recent RCTs and meta-analyses highlighting their renal (especially in septic patients) and coagulopathic side effects, as well as a lack of specific indications for their use
  ▪ colloids are being used based on mechanistic and experimental evidence but there is a paucity of definitive studies investigating their safety and efficacy; routine use of colloids should be avoided

Table 5. IV Fluid Solutions

<table>
<thead>
<tr>
<th>ECF</th>
<th>Ringer’s Lactate</th>
<th>0.9% NS</th>
<th>0.45% NS in D5W</th>
<th>D5W</th>
<th>2/3 D5W + 1/3 NS</th>
<th>Plasmalyte</th>
</tr>
</thead>
<tbody>
<tr>
<td>mEq/L</td>
<td>Na⁺</td>
<td>142</td>
<td>130</td>
<td>154</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>K⁺</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Ca²⁺</td>
<td>4</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Mg²⁺</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Cl⁻</td>
<td>103</td>
<td>109</td>
<td>154</td>
<td>77</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>HCO₃⁻</td>
<td>27</td>
<td>28*</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>mOsm/L</td>
<td>280-310</td>
<td>273</td>
<td>308</td>
<td>154</td>
<td>252</td>
<td>269</td>
</tr>
<tr>
<td>pH</td>
<td>7.4</td>
<td>6.5</td>
<td>5.0</td>
<td>4.5</td>
<td>4.0</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*Converted from lactate

Table 6. Colloid HES Solutions

<table>
<thead>
<tr>
<th>Concentration</th>
<th>Plasma Volume Expansion</th>
<th>Duration (h)</th>
<th>Maximum Daily Dose (mL/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voluven®</td>
<td>6%</td>
<td>1:1</td>
<td>4-6</td>
</tr>
<tr>
<td>Pentaspan®</td>
<td>10%</td>
<td>1:1.2-1.5</td>
<td>18-24</td>
</tr>
</tbody>
</table>

Blood Products

• see Hematology, H52

Red Blood Cells (RBCs)

1 U RBCs (approx. 300 ml) increases Hb by approximately 10 g/L in a 70 kg patient
RBCs may be diluted with colloidal/crystalloid to decrease viscosity
decision to transfuse based on initial blood volume, premorbid Hb level, present volume status, expected further blood loss, patient health status, patient consent
massive transfusion ≥1 x blood volume/24 h

Autologous RBCs

replacement of blood volume with one’s own RBCs
may decrease complications (infectious, febrile, etc.)
alternative to homologous transfusion in elective procedures, but only if adequate Hb and no infection
pre-operative phlebotomy prior to elective surgery (up to 3U collected 3-5 wk before surgery)
intraoperative salvage and filtration (cell saver); contraindicated in contaminated (e.g. bowel, abscess) or cancer cases

Non-RBC Products

• fresh frozen plasma (FFP)
  ▪ contains all plasma clotting factors and fibrinogen close to normal plasma levels
to prevent/treat bleeding due to coagulation factor depletion/deficiencies, liver impairment
cryoprecipitate
  ▪ contains Factors VIII and XIII, von Willebrand Factor (vWF), fibrinogen
platelets
  ▪ used in thrombocytopenia, massive transfusions, impaired platelet function
albumin
  ▪ selective intravascular volume expander
erthropoietin
  ▪ can be used pre-operatively to stimulate erythropoiesis

Complications Due to Transfusion

• infectious risks: HIV, hepatitis B/C, Epstein-Barr virus (EBV), cytomegalovirus (CMV), brucellosis, malaria, salmonellosis, measles, syphilis
• hypervolemia
electrolyte changes: increased K⁺ in stored blood
dilutional coagulopathy

Transfusion Infection Risks

<table>
<thead>
<tr>
<th>Virus</th>
<th>Risk per unit pRBCs</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>1 in 8-12 million</td>
</tr>
<tr>
<td>Hepatitis C virus</td>
<td>1 in 5-7 million</td>
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<tr>
<td>HTLV</td>
<td>1 in 1-3.3 million</td>
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<tr>
<td>Syphilis</td>
<td>&lt;1 in 100 million</td>
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<tr>
<td>West Nile virus</td>
<td>No cases since 2003</td>
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Transfusion and risk of infection in Canada: Update 2012, Paediatr Child Health 2012;17:e102-e111

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Transfusion and risk of infection in Canada: Update 2012, Paediatr Child Health 2012;17:e102-e111
• dilutional thrombocytopenia
• hypothermia
• citrate toxicity
• hypocalcemia
• iron overload
• transfusion-related immunosuppression: perioperative transfusion may be associated with increased risk of post-operative infection, increased short-term mortality and possible cancer recurrence
• see Hematology, H54 for list of transfusion reactions

Induction

Routine Induction vs. Rapid Sequence Induction

- routine induction is the standard in general anesthesia, however a RSI is indicated in patients at risk of regurgitation/aspiration (see Aspiration, A5)
- RSI uses pre-determined doses of induction drugs given in rapid succession to minimize time patient is at risk for aspiration

Table 7. Comparison of Routine Induction vs. RSI

<table>
<thead>
<tr>
<th>Steps</th>
<th>Routine Induction</th>
<th>RSI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Equipment Preparation</td>
<td>Check equipment, drugs, suction, and monitors; prepare an alternative laryngoscope blade and a second ETT tube one size smaller</td>
<td>Check equipment, drugs, suction, and monitors; prepare an alternative laryngoscope blade and a second ETT tube one size smaller</td>
</tr>
<tr>
<td>2. Pre-Oxygenation/Denitrogenation</td>
<td>100% O₂ for 3 min or 4 vital capacity breaths</td>
<td>100% O₂ for 3 min or 4 vital capacity breaths</td>
</tr>
<tr>
<td>3. Pre-Treatment Agents</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation 3 min prior to laryngoscopy</td>
<td>Use agent of choice to blunt physiologic responses to airway manipulation; if possible, give 3 min prior to laryngoscopy, but can skip this step in an emergent situation</td>
</tr>
<tr>
<td>4. Induction Agents</td>
<td>Use IV or inhalation induction agent of choice</td>
<td>Use pre-determined dose of fast acting induction agent of choice</td>
</tr>
<tr>
<td>5. Muscle Relaxants</td>
<td>Muscle relaxant of choice given after the onset of the induction agent</td>
<td>Pre-determined dose of fast acting muscle relaxant (e.g. SCh) given IMMEDIATELY after induction agent</td>
</tr>
<tr>
<td>6. Ventilation</td>
<td>Bag-mask ventilation</td>
<td>DO NOT bag ventilate – can increase risk of aspiration</td>
</tr>
<tr>
<td>7. Cricoid Pressure</td>
<td>Backwards upwards rightwards pressure (BURP) on thyroid cartilage to assist visualization if indicated</td>
<td>Sellick maneuver, also known as cricoid pressure, to prevent regurgitation and assist in visualization (2 kg pressure with drowsiness, 3 kg with loss of consciousness)</td>
</tr>
<tr>
<td>8. Intubation</td>
<td>Intubate, inflate cuff, confirm ETT position</td>
<td>Intubate once paralyzed (~45 s after SCh given), inflate cuff, confirm ETT position; cricoid pressure maintained until ETT cuff inflated and placement confirmed</td>
</tr>
</tbody>
</table>

Induction Agents

- induction in general anesthesia may be achieved with intravenous agents, volatile inhalation agents, or both

Intravenous Agents

- see Table 10, A27
- IV induction agents are non-opioid drugs used to provide hypnosis, amnesia and blunt reflexes
- these are initially used to draw the patient into the maintenance phase of general anesthesia rapidly, smoothly and with little adverse effects
- examples include propofol, sodium thiopental (not available in North America), or ketamine
- a continuous propofol infusion may also be used for the maintenance phase of GA

Solubility of Volatile Anesthetics in Blood

Least Soluble to Most Soluble

Nitrous oxide < desflurane < sevoflurane < isoflurane < halothane
Volatile Inhalational Agents
- examples include sevoflurane, desflurane, isoflurane, enflurane, halothane, and nitrous oxide
- see Table 13, A28

MAC (Minimum Alveolar Concentration)
- the alveolar concentration of a volatile anesthetic at one atmosphere (atm) of pressure that will prevent movement in 50% of patients in response to a surgical stimulus (e.g. abdominal incision)
- 1.2-1.3 times MAC will often ablate response to stimuli in the general population
- potency of inhalational agents is compared using MAC
- MAC values are roughly additive when mixing N₂O with another volatile agent; however, this only applies to movement, not other effects such as BP changes (e.g. 0.5 MAC of a potent agent + 0.5 MAC of N₂O = 1 MAC of potent agent)
- MAC-intubation: the MAC of anesthetic that will inhibit movement and coughing during endotracheal intubation, generally 1.3 MAC
- MAC-block adrenergic response (MAC-BAR): the MAC necessary to blunt the sympathetic response to noxious stimuli, generally 1.5 MAC
- MAC-awake: the MAC of a given volatile anesthetic at which a patient will open their eyes to command, usually 0.3-0.4 of the usual MAC value

Muscle Relaxants and Reversing Agents
- two types of muscle relaxants
  1. depolarizing muscle relaxants: succinylcholine (SCh)
  2. non-depolarizing muscle relaxants: rocuronium, mivacurium, vecuronium, cistracurium, pancuronium
- see Tables 14 and 15, A29 for more details including mechanism of action
- block nicotinic cholinergic receptors in NMJ
- provides skeletal muscle paralysis, including the diaphragm, but spares involuntary muscles such as the heart and smooth muscle
- never use muscle relaxants without adequate preparation and equipment to maintain airway and ventilation
- muscle relaxation produces the following desired effects
  1. facilitates intubation
  2. assists with mechanical ventilation
  3. prevents muscle stretch reflex and decreases muscle tone
  4. allows access to the surgical field (intracavitary surgery)
- nerve stimulator (i.e. train of four) is used intraoperatively to assess the degree of nerve block; no twitch response seen with complete neuromuscular blockade
Reversing Agents
- neostigmine, pyridostigmine, edrophonium (see Table 16, A30)
- reversal agents are acetylcholinesterase inhibitors
  - inhibits enzymatic degradation of ACh; increases amount of ACh at nicotinic and muscarinic receptors, displacing non-depolarizing muscle relaxant
  - administer reversal agents when there has been some recovery of blockade (i.e. muscle twitch)
  - can only reverse the effect of non-depolarizing muscle relaxants
- anticholinergic agents (e.g. atropine, glycopyrrolate) are simultaneously administered to minimize muscarinic effect of reversal agents (i.e. bradycardia, salivation and increased bowel peristalsis)

Analgesia
- options include opioids (e.g. morphine, fentanyl, hydromorphone), NSAIDS, acetaminophen, ketamine, gabapentin, local, and regional anesthetic (see Table 11, A28)

Maintenance
- general anesthesia is maintained using volatile inhalation agents and/or IV agents (i.e. propofol infusion)
- analgesia (usually IV opioids) and muscle relaxants are also given as needed

Extubation
- criteria
  - patient must no longer have intubation requirements (see Table 2, A7)
  - patency: airway must be patent
  - protection: airway reflexes intact
  - patient must be oxygenating and ventilating spontaneously
- general guidelines
  - ensure patient has normal neuromuscular function (peripheral nerve stimulator monitoring) and hemodynamic status
  - ensure patient is breathing spontaneously with adequate rate and tidal volume
  - allow ventilation (spontaneous or controlled) with 100% O₂ for 3-5 min
  - suction secretions from pharynx
  - deflate cuff, remove ETT on inspiration (vocal cords abducted)
  - ensure patient is breathing adequately after extubation
  - ensure face mask for O₂ delivery available
  - proper positioning of patient during transfer to recovery room (supine, head elevated)

Complications of Extubation
- early extubation: aspiration, laryngospasm
- late extubation: transient vocal cord incompetence, edema (glottic, subglottic), pharyngitis, tracheitis

Laryngospasm
- defined as forceful involuntary spasm of laryngeal muscles caused by stimulation of superior laryngeal nerve (by oropharyngeal secretions, blood, extubation)
- causes partial or total airway obstruction
- more likely to occur in semi-conscious patients
- prevention: extubate while patient is still deeply under anesthesia or fully awake
- treatment: apply sustained positive pressure with bag-mask ventilation with 100% oxygen, low-dose propofol (0.5-1.0 mg/kg) optional, low-dose succinylcholine (approximately 0.25 mg/kg) and reintubation if hypoxia develops
Regional Anesthesia

- local anesthetic agent (LA) applied around a peripheral nerve at any point along the length of the nerve (from spinal cord up to, but not including, the nerve endings) for the purpose of reducing or preventing impulse transmission
- no CNS depression (unless overdose of local anesthetic); patient remains conscious
- regional anesthetic techniques categorized as follows:
  - epidural and spinal anesthesia (neuraxial anesthesia)
  - peripheral nerve blocks
  - IV regional anesthesia (e.g. Bier block)

Patient Preparation
- sedation may be indicated before block
- monitoring should be as extensive as for general anesthesia

Relative Indications for Regional Anesthesia
- patient preference
- superior post-operative analgesia
- decreased incidence of PONV
- shorter recovery and improved rehabilitation
- general anesthesia not available/contraindicated
- differential blockade (to block pain but preserve motor function)

Complications of Regional Anesthesia
- failure of technique/inadequate anesthesia
- unintentional total spinal anesthesia
- systemic drug toxicity due to overdose or intravascular injection (see Local Anesthesia, A21)
- injury to nerve root/spinal cord (nerve deficit), epidural vein (hematoma), peripheral nerve (intraneural injection)
- infection (e.g. osteitis, epidural abscess, meningitis)

Epidural and Spinal Anesthesia

- most useful for surgeries performed below level of umbilicus

Anatomy of Spinal/Epidural Area
- spinal cord extends to L2, dural sac to S2 in adults
- nerve roots (cauda equina) from L2 to S2
- needle inserted below L2 should not encounter cord, thus L3-L4, L4-L5 interspace commonly used
- structures penetrated
  - skin
  - subcutaneous fat
  - supraspinous ligament
  - interspinous ligament
  - ligamentum flavum (last layer before epidural space)
  - dura + arachnoid for spinal anesthesia

Table 8. Epidural vs. Spinal Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Epidural</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deposition Site</strong></td>
<td>LA injected in epidural space (space between ligamentum flavum and dura)</td>
<td>LA injected into subarachnoid space in the dural sac surrounding the spinal cord and nerve roots</td>
</tr>
<tr>
<td><strong>Onset</strong></td>
<td>Significant blockade requires 10-15 min Slower onset of side effects</td>
<td>Rapid blockade (onset in 2-5 min)</td>
</tr>
<tr>
<td><strong>Effectiveness</strong></td>
<td>Effectiveness of blockade can be variable</td>
<td>Very effective blockade</td>
</tr>
<tr>
<td><strong>Difficulty</strong></td>
<td>Technically more difficult; greater failure rate</td>
<td>Easier to perform due to visual confirmation of CSF flow</td>
</tr>
<tr>
<td><strong>Patient Positioning</strong></td>
<td>Position of patient not as important; specific gravity not an issue</td>
<td>Hyperbaric LA solution – position of patient important</td>
</tr>
</tbody>
</table>

Benefits of Regional Anesthesia
- Reduced perioperative pulmonary complications
- Reduced perioperative analgesia requirements
- Decreased PONV
- Ability to monitor CNS status during procedure
- Improved perfusion
- Lower incidence of VTE

Landmarking Epidural/Spinal Anesthesia
- Spinal processes should be maximally flexed
- L4 spinal processes found between iliac crests
- Common sites of insertion are L3-L4 and L4-L5

Classic Presentation of Dural Puncture Headache
- Onset 6 h-3 d after dural puncture
- Postural component (worse sitting)
- Occipital or frontal localization
- ± tinnitus, diplopia
Table 8. Epidural vs. Spinal Anesthesia (continued)

<table>
<thead>
<tr>
<th>Specific Gravity/Spread</th>
<th>Epidural</th>
<th>Spinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>...</td>
<td>LA solution may be made hyperbaric (of greater specific gravity than the cerebrospinal fluid by mixing with 10% dextrose, thus increasing spread of LA to the dependent [low] areas of the subarachnoid space)</td>
<td></td>
</tr>
<tr>
<td>Dosage</td>
<td>Larger volume/dose of LA (usually &gt; toxic IV dose)</td>
<td>Smaller dose of LA required (usually &lt; toxic IV dose)</td>
</tr>
<tr>
<td>Continuous Infusion</td>
<td>Use of catheter allows for continuous infusion or repeat injections</td>
<td>None</td>
</tr>
</tbody>
</table>

- **Complications**
  - Failure of technique
  - Hypotension
  - Bradycardia if cardiac sympathetics blocked (only if ~T2-4 block), e.g. "high spinal"
  - Epidural or subarachnoid hematoma
  - Accidental subarachnoid injection can produce spinal anesthesia (and any of the above complications)
  - Systemic toxicity of LA (accidental intravenous)
  - Catheter complications (shearing, kinking, vascular or subarachnoid placement)
  - Infection
  - Dural puncture

- **Combined Spinal-Epidural**
  - Combines the benefits of rapid, reliable, intense blockade of spinal anesthesia together with the flexibility of an epidural catheter

**Contraindications to Spinal/Epidural Anesthesia**
- **absolute contraindications**
  - Lack of trained personnel
  - Lack of resuscitative drugs/equipment
  - Patient refusal
  - Allergy to local anesthetic
  - Infection at puncture site or underlying tissues
  - Coagulopathies/bleeding diathesis
  - Raised ICP
  - Sepsis/bacteremia
  - Severe hypovolemia
  - Cardiac lesion with fixed output states (severe mitral/aortic stenosis)
  - Lack of IV access
- **relative contraindications**
  - Pre-existing neurological disease (demyelinating lesions)
  - Previous spinal surgery, severe spinal deformity
  - Prolonged surgery
  - Major blood loss or maneuvers that can compromise reaction

**Peripheral Nerve Blocks**
- Deposition of LA around the target nerve or plexus
- Ultrasound guidance and peripheral nerve stimulation (needle will stimulate target nerve/plexus) may be used to guide needle to target nerve while avoiding neural trauma or intraneurale injection
- Approximately 2-4 per 10,000 risk of late neurologic injury
- Most major nerves or nerve plexi can be targeted (brachial plexus block, femoral nerve block, sciatic nerve block, etc.)
- Performed with standard monitors
- Resuscitation equipment must be available

**Contraindications to Peripheral Nerve Blockade**
- **Absolute contraindications**
  - Allergy to LA
  - Patient refusal
- **Relative contraindications**
  - Certain types of pre-existing neurological dysfunction (e.g. ALS, MS, diabetic neuropathy)
  - Local infection at block site
  - Bleeding disorder

---

**Figure 9. Landmarks for placement of epidural/spinal**

**Reduction of Post-Operative Mortality**

- **Purpose**: To obtain reliable estimates of the effects of neuraxial blockade with epidural or spinal anesthesia on post-operative morbidity and mortality after various surgeries with or without general anesthesia.
- **Study**: Systematic review of all trials with randomization to intraoperative neuraxial blockade vs. control group.
- **Patients**: 141 trials including 9,569 patients.
- **Main Outcomes**: All cause mortality, MI, PE, DVT, transfusion requirements, pneumonia, other infections, respiratory depression, and renal failure.
- **Results**: With neuraxial blockade, overall mortality was reduced by about one third. Neuraxial blockade reduced the risk of PE by 55%, DVT by 44%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59%. There were also reductions in MI and renal failure. These mortality reductions are irrespective of surgical group, type of blockade (epidural or spinal), or whether neuraxial blockade was combined with general anesthesia.
- **Conclusions**: Neuraxial blockade reduces post-operative mortality and other serious complications.
Local Anesthesia

Local Anesthetic Agents

- see Table 17, A29 for list of LA agents

Definition and Mode of Action
- LA are drugs that block the generation and propagation of impulses in excitable tissues: nerves, skeletal muscle, cardiac muscle, brain
- LA bind to receptors on the cytosolic side of the Na⁺ channel, inhibiting Na⁺ flux and thus blocking impulse conduction
- different types of nerve fibres undergo blockade at different rates

Absorption, Distribution, Metabolism
- LA readily crosses the blood-brain barrier (BBB) once absorbed into the bloodstream
- ester-type LA (procaine, tetracaine) are broken down by plasma and hepatic esterases; metabolites excreted via kidneys
- amide-type LA (lidocaine, bupivicaine) are broken down by hepatic mixed-function oxidases (P450 system); metabolites excreted via kidneys

Selection of LA
- choice of LA depends on
  ▪ onset of action: influenced by pKa (the lower the pKa, the higher the concentration of the base form of the LA, and the faster the onset of action)
  ▪ duration of desired effects: influenced by protein binding (longer duration of action when protein binding of LA is strong)
  ▪ potency: influenced by lipid solubility (agents with high lipid solubility penetrate the nerve membrane more easily)
  ▪ unique needs (e.g. sensory blockade with relative preservation of motor function by bupivicaine at low doses)
  ▪ potential for toxicity

Systemic Toxicity

- see Table 17, A29 for maximum doses, potency, and duration of action for common LA agents
- occurs by accidental intravascular injection, LA overdose, or unexpectedly rapid absorption
- CNS effects
  ▪ CNS effects first appear to be excitatory due to initial block of inhibitory fibres, then subsequent block of excitatory fibres
  ▪ effects in order of appearance
    ▪ numbness of tongue, perioral tingling, metallic taste
    ▪ disorientation, drowsiness
    ▪ tinnitus
    ▪ visual disturbances
    ▪ muscle twitching, tremors
    ▪ unconsciousness
    ▪ convulsions, seizures
    ▪ generalized CNS depression, coma, respiratory arrest
- CVS effects
  ▪ vasodilation, hypotension
  ▪ decreased myocardial contractility
  ▪ dose-dependent delay in cardiac impulse transmission
    ▪ prolonged PR, QRS intervals
    ▪ sinus bradycardia
  ▪ CVS collapse
- treatment of systemic toxicity
  ▪ early recognition of signs, get help
  ▪ 100% O₂, manage ABCs
  ▪ diazepam or sodium thiopental may be used to increase seizure threshold
  ▪ manage arrhythmias (see ACLS Guidelines, A32)
  ▪ Intralipid* 20% to bind local anesthetic in circulation

Figure 10. Local anesthetic systemic toxicity
Local Infiltration and Hematoma Blocks

Local Infiltration
- injection of tissue with LA, producing a lack of sensation in the infiltrated area due to LA acting on nerves
- suitable for small incisions, suturing, excising small lesions
- can use fairly large volumes of dilute LA to infiltrate a large area
- low concentrations of epinephrine (1:100,000–1:200,000) cause vasoconstriction, thus reducing bleeding and prolonging the effects of LA by reducing systemic absorption

Fracture Hematoma Block
- special type of local infiltration for pain control during manipulation of certain fractures
- hematoma created by fracture is infiltrated with LA to anesthetize surrounding tissues
- sensory blockade may only be partial
- no muscle relaxation

Topical Anesthetics
- various preparations of local anesthetics available for topical use, may be a mixture of agents (EMLA cream is a combination of 2.5% lidocaine and prilocaine)
- must be able to penetrate the skin or mucous membrane

Post-Operative Care
- pain management should be continuous from OR to post-anesthetic care unit (PACU) to hospital ward and home

Common Post-Operative Anesthetic Complications

Nausea and Vomiting
- hypotension and bradycardia must be ruled out
- pain and surgical manipulation also cause nausea
- often treated with dimenhydrinate (Gravol®), metoclopramide (Maxeran®; not with bowel obstruction), prochlorperazine (Stemetil®), ondansetron (Zofran®), granisetron (Kytril®)
- metabolic disturbance (hypoglycemia, hypercalcemia, hyponatremia – especially post-TURP)
- drug effect (ketamine, anticholinergics, serotonin)
- elderly patients are more susceptible to post-operative delirium

Confusion and Agitation
- ABCs first – confusion or agitation can be caused by airway obstruction, hypercapnea, hypoxemia
- neurologic status (Glasgow Coma Scale, pupils), residual paralysis from anesthetic
- fear/anxiety/separation from caregivers, language barriers
- reduced cardiac output (hypovolemia, most common cause) and/or peripheral vasodilation
- drug effect (ketamine, anticholinergics, serotonin)
- elderly patients are more susceptible to post-operative delirium

Respiratory Complications
- susceptible to aspiration of gastric contents due to PONV and unreliable airway reflexes
- airway obstruction (secondary to reduced muscle tone from residual anesthetic, soft tissue trauma and edema, or pooled secretions) may lead to inadequate ventilation, hypoxemia, and hypercapnia
- airway obstruction can often be relieved with head tilt, jaw elevation, and anterior displacement of the mandible. If the obstruction is not reversible, a nasal or oral airway may be used

Hypotension
- must be identified and treated quickly to prevent inadequate perfusion and ischemic damage
- reduced cardiac output (hypovolemia, most common cause) and/or peripheral vasodilation (residual anesthetic agent)
- first step in treatment is usually the administration of fluids ± inotropic agents

Hypertension
- pain, hypercapnia, hypoxemia, increased intravascular fluid volume, and sympathomimetic drugs can cause hypertension
- sodium nitroprusside or β-blocking drugs (e.g. esmolol and metoprolol) can be used to treat hypertension

Where Not to Use LA with Epinephrine
“Ears, Fingers, Toes, Penis, Nose”

Risk Factors for Post-Operative Nausea and Vomiting (PONV)
- Young age
- Female
- History of PONV
- Non-smoker
- Type of surgery: ophtho, ENT, abdo/pelvic, plastics
- Type of anesthetic: N2O, opioids, volatile agents

Drugs for Preventing Post-Operative Nausea and Vomiting
Cochrane DB Syst Rev 2006;3:CD004125
Purpose: To evaluate the efficacy of antiemetics in preventing PONV
Methods: A meta-analysis was performed looking at randomized controlled trials comparing an antiemetic to either a second antiemetic or placebo. Trials looking at dosing and/or timing of medication administration were also included. PONV was used as the primary outcome.
Results: 737 studies involving 103,237 patients. Eight drugs significantly reduced the occurrence of PONV, namely: droperidol, metoclopramide, ondansetron, tropisetron, dolasetron, dexamethasone, cyclizine, and granisetron. Relative risk (RR) versus placebo varied between 0.67 and 0.80. Side effects included a significant increase in drowsiness for droperidol (RR 1.32) and headache for ondansetron (RR 1.16). The cumulative number needed to treat was 3.5.
Conclusion: Antiemetic medication is effective for reducing the occurrence of PONV. However, further investigation needs to be done to determine whether antiemetics can cause more severe (and likely rare) side effects, which could alter how liberally they are used.
## Pain Management

### Definitions
- **pain**: perception of nociception, which occurs in the brain
- **nociception**: detection, transduction, and transmission of noxious stimuli

### Pain Classifications
- **temporal**: acute vs. chronic
- **mechanism**: nociceptive vs. neuropathic

### Acute Pain
- pain of short duration (<6 wk) usually associated with surgery, trauma, or acute illness; often associated with inflammation
- usually limited to the area of damage/trauma and resolves with healing

## Pharmacological Management of Acute Pain
- ask the patient to rate the pain out of 10, or use visual analog scale, to determine severity
- pharmacological treatment guided by WHO analgesia ladder
- patient controlled analgesia (PCA)
  - involves the use of computerized pumps that can deliver a constant infusion as well as bolus breakthrough doses of parenterally-administered opioid analgesics
  - limited by lockout intervals
  - most commonly used agents: morphine and hydromorphone
  - see Table 12, A28 for suggested infusion rate, PCA dose and lockout intervals

### Table 9. Commonly Used Analgesics

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Tylenol</em>®</td>
<td><em>Aspirin</em>, ibuprofen, naproxen ketorolac (IV)</td>
<td>Orally: codeine, oxycodone, morphine, hydromorphone Parenterally: morphine, hydromorphone, fentanyl</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>First-line for mild acute pain</td>
<td>Unclear, hypothesized cyclooxygenase-2 (COX-2) inhibition Unclear, hypothesized modulation of endogenous cannabinoid system</td>
</tr>
<tr>
<td>Mild-moderate pain</td>
<td>Non-selective COX-1 and 2 inhibition reducing proinflammatory prostaglandin synthesis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Opioid Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parenteral (IV)</td>
</tr>
<tr>
<td>Morphine</td>
</tr>
<tr>
<td>Hydromorphone</td>
</tr>
<tr>
<td>Codeine</td>
</tr>
<tr>
<td>Oxycodone</td>
</tr>
<tr>
<td>Fentanyl IV</td>
</tr>
</tbody>
</table>

- **Opioid for moderate to severe pain**
  - (e.g. morphine)
  - ± Non-opiod, ± Adjuvant

- **Opioid for mild to moderate pain**
  - (e.g. codeine)
  - ± Non-opiod, ± Adjuvant

- **Non-opiod (e.g. NSAID)**
  - ± Non-opiod, ± Adjuvant

### Opioid Conversion

<table>
<thead>
<tr>
<th>Drug</th>
<th>Parenteral Dose</th>
<th>Oral Equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>30 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>4 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>120 mg</td>
<td>200 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>N/A</td>
<td>20 mg</td>
</tr>
<tr>
<td>Fentanyl IV</td>
<td>120 μg</td>
<td>N/A</td>
</tr>
</tbody>
</table>

- **Cautionary Use of NSAIDs in Patients with**
  - Asthma
  - Coagulopathy
  - G.I ulcers
  - Renal insufficiency
  - Pregnancy, 3rd trimester

- **Common Side Effects of Opioids**
  - N/V
  - Constipation
  - Sedation
  - Pruritus
  - Abdominal pain
  - Urinary retention
  - Respiratory depression

- When prescribing opioids, consider:
  - Breakthrough dose
  - Anti-emetics
  - Laxative

### PCA Parameters
- **Loading dose**
- **Bolus dose**
- **Lockout interval**
- **Continuous infusion (optional)**
- **Maximum 4 h dose (limit)**

- **Advantages of PCA**
  - Improved patient satisfaction
  - Fewer side effects
  - Accomodates patient variability
  - Accomodiates changes in opioid requirements

---

### Figure 11. Acute pain mechanism

- Tissue damage by: thermal, chemical, mechanical forces
- Nociceptors detect pain stimulus
- 1st order afferent neuron
- 2nd order afferent neuron
- Dorsal horn of spinal cord
- Sensory cortex
- Ventral posterior lateral nucleus of thalamus

### Figure 12. WHO analgesia ladder

- Opioid for moderate to severe pain (e.g. morphine)
  - ± Non-opiod, ± Adjuvant

- Opioid for mild to moderate pain (e.g. codeine)
  - ± Non-opiod, ± Adjuvant

- Non-opiod (e.g. NSAID)
  - ± Non-opiod, ± Adjuvant

---

*Note: Images and diagrams are not included in the text representation.*
Table 9. Commonly Used Analgesics (continued)

<table>
<thead>
<tr>
<th>Acetaminophen</th>
<th>NSAIDs</th>
<th>Opioids</th>
</tr>
</thead>
<tbody>
<tr>
<td>limited by analgesic ceiling beyond which there is no additional analgesia</td>
<td>limited by analgesic ceiling beyond which there is no additional analgesia</td>
<td>No analgesic ceiling (except for codeine)</td>
</tr>
<tr>
<td>opioid-sparing</td>
<td>opioid-sparing</td>
<td>can be administered intrathecally (spinal block) or by continuous infusion</td>
</tr>
<tr>
<td>Significant inter-individual variation in efficacy</td>
<td>Significant inter-individual variation in efficacy</td>
<td></td>
</tr>
</tbody>
</table>

Opioid Antagonists (naloxone, naltrexone)
- Indication: opioid overdose (manifests primarily at CNS, e.g. respiratory depression)
- Mechanism of action: competitively inhibit opioid receptors, predominantly μ receptors
  - Naloxone is short-acting (t1/2 = 1 h); effects of narcotic may return when naloxone wears off; therefore, the patient must be observed closely following its administration
  - Naltrexone is longer-acting (t1/2 = 10 h); less likely to see return of opioid effects
- Side effects: relative overdose of naloxone may cause nausea, agitation, sweating, tachycardia, hypertension, re-emergence of pain, pulmonary edema, seizures (essentially opioid withdrawal)
  - Resistant to allodynia (pain in response to normally painless stimuli) or hyperalgesia (increased sensitivity to painful stimuli)
  - Consider adding anticonvulsants (gabapentin, pregabalin) or low-dose tricyclic antidepressant as combination, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity
  - Patient is positioned in left uterine displacement using a wedge under her right flank
  - Cesarean delivery
  - Breastfeeding difficulties, long-term back pain, or long-term urinary incontinence.

Neuropathic Pain
- Pain caused by peripheral or central nervous system injury, often described as burning, lancinating, shooting, or tingling
- Nociceptive and neuropathic components; dysregulation of analgesic pathways
- In the peripartum period, consider continuing regular long-acting analgesics and augmenting with regional techniques, adjuvants, additional opioid analgesia and non-pharmacological techniques

Obstetric Anesthesia

Physiologic Changes in Pregnancy
- Airway
  - Possible difficult airway as tissues becomes edematous and friable especially in labour
- Respiratory
  - Decreased FRC and increased O2 consumption → desaturation occurs more quickly during apnea
- Cardiovascular system
  - Increased blood volume > increased RBC mass → mild anemia
  - Decreased SVR proportionately greater than increased CO → decreased BP
- Prone to decreased BP due to aortocaval compression – therefore for surgery, a pregnant patient is positioned in left uterine displacement using a wedge under her right flank
- Central nervous system
  - Decreased MAC due to hormonal effects
  - Increased block height due to engorged epidural veins
- Gastrointestinal system
  - Delayed gastric emptying
  - Increased volume and acidity of gastric fluid
  - Decreased LES tone
  - Increased abdominal pressure

Combined, these lead to an increased risk of aspiration – therefore for surgery, a pregnant patient is given sodium citrate 30 cc PO immediately before surgery to neutralize gastric acidity
Options for Analgesia during Labour
- psychoprophylaxis – Lamaze method
  - patterns of breathing and focused attention on fixed object
- systemic medication
  - easy to administer, but risk of maternal or neonatal depression
  - opioids most commonly used if delivery is not expected within 4 h
- inhalational analgesia
  - easy to administer, makes uterine contractions more tolerable, but does not relieve pain completely
  - 50% nitrous oxide
- neuraxial anesthesia
  - provides excellent analgesia with minimal depressant effects
  - hypotension is the most common complication
  - maternal BP monitored q2-5 min for 15-20 min after initiation and regularly thereafter
  - epidural usually given as it preferentially blocks sensation, leaving motor function intact

Options for Caesarean Section
- neuraxial: spinal or epidural
- general: used if contraindications or time precludes regional blockade

Pediatric Anesthesia

Respiratory System
- in comparison to adults, anatomical differences in infants include:
  - large head, short trachea/neck, large tongue, adenoids, and tonsils
  - narrow nasal passages (obligate nasal breathers until 5 mo)
  - narrowest part of airway at the level of the cricoid vs. glottis in adults
  - epiglottis is longer, U shaped and angled at 45°; carina is wider and is at the level of T2 (T4 in adults)
- physiologic differences include
  - faster RR, immature respiratory centres which are depressed by hypoxia/hypercapnea (airway closure occurs in the neonate at the end of expiration)
  - less oxygen reserve during apnea – decreased total lung volume, vital and functional reserve capacity together with higher metabolic needs
  - greater V/Q mismatch – lower lung compliance due to immature alveoli (mature at 8 yr)
  - greater work of breathing – greater chest wall compliance, weaker intercostals/diaphragm, and higher resistance to airflow

Cardiovascular System
- blood volume at birth is approximately 80 mL/kg; transfusion should be started if >10% of blood volume lost
- children have a high HR and low BP
- CO is dependent on HR, not stroke volume because of low heart wall compliance; therefore, bradycardia → severe compromise in CO

Temperature Regulation
- vulnerable to hypothermia
- minimize heat loss by use of warming blankets, covering the infant’s head, humidification of inspired gases, and warming of infused solutions

Central Nervous System
- MAC of halothane is increased compared to the adult (0.75% adult, 1.2% infant, 0.87% neonate)
- NMJ is immature for the first 4 wk of life and thus there is an increased sensitivity to non-depolarizing relaxants
- parasymptethetics mature at birth, sympthetics mature at 4-6 mo → autonomic imbalance
- infant brain is 12% of body weight and receives 34% of CO (adult: 2% body weight and 14% CO)

Glucose Maintenance
- infants less than 1 yr old can become seriously hypoglycemic during pre-operative fasting and post-operatively if feeding is not recommened as soon as possible
- after 1 yr, children are able to maintain normal glucose homeostasis in excess of 8 h

Pharmacology
- higher dose requirements because of higher TBW (75% vs. 60% in adults) and greater volume of distribution
- barbiturates/opioids more potent due to greater permeability of BBB
Uncommon Complications

Malignant Hyperthermia

- hypermetabolic disorder of skeletal muscle
- due to an uncontrolled increase in intracellular Ca\(^{2+}\) (because of an anomaly of the ryanodine receptor which regulates the Ca\(^{2+}\) channel in the sarcoplasmic reticulum of skeletal muscle)
- autosomal dominant inheritance
- incidence of 1-5 in 100,000, may be associated with skeletal muscle abnormalities such as dystrophy or myopathy
- anesthetic drugs triggering MH include
  - all inhalational agents except nitrous oxide
  - depolarizing muscle relaxants: SCh

Clinical Picture

- onset: immediate or hours after contact with trigger agent
  - increased oxygen consumption
  - increased ET\(_{CO_2}\) on capnograph
  - tachycardia/dysrhythmia
  - tachypnea/cyanosis
  - diaphoresis
  - hypertension
  - increased temperature (late sign)
- muscular symptoms
  - trismus (masseter spasm) common but not specific for MH (occurs in 1% of children given SCh with halothane anesthesia)
  - tender, swollen muscles due to rhabdomyolysis
  - trunk or total body rigidity

Complications

- coma
- DIC
- rhabdomyolysis
- myoglobinuric renal failure/hepatic dysfunction
- electrolyte abnormalities (e.g. hyperkalemia) and secondary arrhythmias
- ARDS
- pulmonary edema
- can be fatal if untreated

Prevention

- suspect MH in patients with a family history of problems/death with anesthetic
- avoid all trigger medications, use vapour free equipment, use regional anesthesia if possible
- central body temp and ET\(_{CO_2}\) monitoring

Malignant Hyperthermia Management (Based on Malignant Hyperthermia Association of the U.S. [MHAUS] Guidelines, 2008)

1. notify surgeon, discontinue volatile agents and succinylcholine, hyperventilate with 100% oxygen at flows of 10 L/min or more, halt the procedure as soon as possible
2. dantrolene 2.5 mg/kg IV, through large-bore IV if possible
   - repeat until there is control of signs of MH; sometimes up to 30 mg/kg is necessary
3. bicarbonate 1-2 mEq/kg if blood gas values are not available for metabolic acidosis
4. cool patients with core temperature >39°C
   - lavage open body cavities, stomach, bladder, rectum; apply ice to surface; infuse cold saline IV
   - stop cooling if temperature is <38°C to prevent drift to <36°C
5. dysrhythmias usually respond to treatment of acidosis and hyperkalemia
   - use standard drug therapy except Ca\(^{2+}\) channel blockers as they may cause hyperkalemia and cardiac arrest in presence of dantrolene

ET T Sizing in Pediatrics

<table>
<thead>
<tr>
<th>Diameter (mm) of tracheal tube in children after 1 year</th>
<th>= (age/4) + 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length (cm) of tracheal tube</td>
<td>= (age/2) + 12</td>
</tr>
</tbody>
</table>

Basic Principles of MH Management

"Some Hot Dude Better Get Iced Fluids Fast"

Stop all triggering agents, give 100% \(O_2\)
Hyperventilate
Dantrolene 2.5 mg/kg every 5 min
Bicarbonate
Glucose and insulin
IV fluids; cool patient to 38°C
Fluid output; consider furosemide
Tachycardia: be prepared to treat VT
6. hyperkalemia
   - treat with hyperventilation, bicarbonate, glucose/insulin, calcium
   - bicarbonate 1-2 mEq/kg IV, calcium chloride 10 mg/kg or calcium gluconate 10-50 mg/kg
     for life-threatening hyperkalemia and check glucose levels hourly
7. follow ETCO2, electrolytes, blood gases, creatine kinase (CK), core temperature, urine output/colour with Foley catheter, coagulation studies
   - if CK and/or potassium rises persistently or urine output falls to <0.5 mL/kg/h, induce
clearance to >1 mL/kg/h urine to avoid myoglobinuric renal failure
8. maintain anesthesia with benzodiazepines, opioids, and propofol
9. transfer to ICU bed

Abnormal Pseudocholinesterase

- pseudocholinesterase hydrolyzes SCh and mivacurium
- individuals with abnormal pseudocholinesterase will have prolonged muscular blockade
- SCh and mivacurium are contraindicated in those with abnormal pseudocholinesterase
- if SCh or mivacurium are given accidentally, treat with mechanical ventilation until function returns to normal (do not use cholinesterase inhibitors)

Common Medications

Table 10. Intravenous Induction Agents

<table>
<thead>
<tr>
<th>Propofol (Diprivan®)</th>
<th>Thiopental (sodium thiolental, sodium thioptone)</th>
<th>Ketamine (Ketalar®, Ketaject®)</th>
<th>Benzodiazepines (midazolam [Versed®], diazepam [Valium®], lorazepam [Ativan®])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class</td>
<td>Alkylphenol – hypnotic</td>
<td>Ultra-short acting thiobarbiturate – hypnotic</td>
<td>Benzodiazepines – anxiolytic</td>
</tr>
<tr>
<td>Action</td>
<td>Inhibitory at GABA synapse</td>
<td>Decreased time Cl- channels open, facilitating GABA and suppressing glutamic acid</td>
<td>May act on NMDA, opiate, and other receptors</td>
</tr>
<tr>
<td></td>
<td>Decreased cerebral metabolic rate and blood flow, decreased ICP, decreased SV, decreased BP, and decreased SV</td>
<td>Decreased cerebral metabolism and blood flow, decreased CPP, decreased CO, decreased BP, decreased reflex tachycardia, decreased respiration</td>
<td>Causes increased glycine inhibitory neurotransmitter, facilitates GABA</td>
</tr>
<tr>
<td>Indications</td>
<td>Induction</td>
<td>Induction</td>
<td>Major trauma, hypovolemia, severe asthma because sympathomimetic</td>
</tr>
<tr>
<td></td>
<td>Maintenance</td>
<td>Control of convulsive states</td>
<td>Used for sedation, amnesia, and amnesticity</td>
</tr>
<tr>
<td></td>
<td>Total intravenous anesthesia (TIVA)</td>
<td></td>
<td>Marked respiratory depression</td>
</tr>
<tr>
<td>Caution</td>
<td>Allergy (egg, soy)</td>
<td>Allergy to barbiturates</td>
<td>Ketamine allergy</td>
</tr>
<tr>
<td></td>
<td>Patients who cannot tolerate sudden decreased BP (e.g. fixed cardiac output or shock)</td>
<td>Uncontrolled hypotension, shock, cardiac failure</td>
<td>TCA medication (interaction causes HTN and dysrhythmias)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Porphyrin, liver disease, status asthmaticus, myxedema</td>
<td>History of psychosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Patients who cannot tolerate HTN (e.g. CHF, increased ICP, aneurysm)</td>
</tr>
<tr>
<td>Dosing</td>
<td>IV induction: 2.5-3.0 mg/kg (less with opioids)</td>
<td>IV induction: 3-5 mg/kg</td>
<td>IV induction 1-2 mg/kg</td>
</tr>
<tr>
<td></td>
<td>Unconscious &lt; 1 min</td>
<td>Unconscious about 30 s</td>
<td>Dissociation in 15 s, analgesia, amnesia, and unconsciousness in 45-60 s</td>
</tr>
<tr>
<td></td>
<td>Lasts 4-6 min</td>
<td>Lasts 5 min</td>
<td>Unconscious for 10-15 min, analgesia for 40 min, amnesia for 1-2 h</td>
</tr>
<tr>
<td></td>
<td>t1/2 = 55 min</td>
<td>Accumulation with repeat dosing – not for maintenance</td>
<td>t1/2 = ~3 h</td>
</tr>
<tr>
<td></td>
<td>Decreased post-operative sedation, recovery time, N/V</td>
<td>t1/2 = 5-10 h</td>
<td>Onset less than 5 min if given IV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-operative sedation lasts hours</td>
<td>Duration of action long but variable/somewhat unpredictable</td>
</tr>
<tr>
<td>Special Considerations</td>
<td>0-30% decreased BP due to vasodilatation</td>
<td>Combining with rocuronium causes precipitates to form</td>
<td>Antagonist: flumazenil (Anexate®)</td>
</tr>
<tr>
<td></td>
<td>Reduce burning at IV site by mixing with lidocaine</td>
<td>High incidence of emergence reactions (vivid dreaming, out-of-body sensation, illusions)</td>
<td>Competitive inhibitor, 0.2 mg IV over 15 s, repeat with 0.1 mg/min (max of 2 mg), t1/2 of 60 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pretreat with glycopyrrolate to decrease salivation</td>
<td>Midazolam also has amnestic (antegrade) effect and decreased risk of thrombophlebitis</td>
</tr>
</tbody>
</table>
Table 11. Opioids

<table>
<thead>
<tr>
<th>Agent</th>
<th>Relative Dose to 10 mg Morphine IV</th>
<th>Moderate Dose</th>
<th>Onset</th>
<th>Duration</th>
<th>Special Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>200 mg PO</td>
<td>15-30 mg PO</td>
<td>Late (30-60 min)</td>
<td>Moderate (4-6 h)</td>
<td>Primarily post-operative use, not for IV use</td>
</tr>
<tr>
<td>Meperidine (Demerol®)</td>
<td>75 mg IV</td>
<td>2-3 mg/kg IV</td>
<td>Moderate (10 min)</td>
<td>Moderate (2-4 h)</td>
<td>Anticholinergic, hallucinations, less pupillary constriction than morphine, metabolite build up may cause seizures</td>
</tr>
<tr>
<td>Morphine</td>
<td>10 mg IV</td>
<td>0.2-0.3 mg/kg IV</td>
<td>Moderate (5-10 min)</td>
<td>Moderate (4-5 h)</td>
<td>Histamine release leading to decrease in BP</td>
</tr>
</tbody>
</table>
| Opioid PCA Doses

<table>
<thead>
<tr>
<th>Agent</th>
<th>PCA Dose</th>
<th>PCA Lockout Interval</th>
<th>PCA 4 h Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>1 mg</td>
<td>5 min</td>
<td>30 mg</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-50 µg</td>
<td>5 min</td>
<td>400 µg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.2 mg</td>
<td>5 min</td>
<td>6 mg</td>
</tr>
</tbody>
</table>

Table 13. Volatile Inhalational Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>MAC (% gas in O2)</th>
<th>CNS</th>
<th>Resp</th>
<th>CVS</th>
<th>MSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sevoflurane</td>
<td>2.0</td>
<td>Increased ICP</td>
<td>Respiratory depression (severely decreased TV, increased RR), decreased response to respiratory CO2 reflexes, bronchodilation</td>
<td>Less decrease of contractility, stable HR</td>
<td>Muscle relaxation, potentiation of other muscle relaxants, uterine relaxation</td>
</tr>
<tr>
<td>Desflurane</td>
<td>6.0</td>
<td>Increased ICP</td>
<td>—</td>
<td>Tachycardia with rapid increase in concentration</td>
<td>—</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.2</td>
<td>Decreased cerebral metabolic rate</td>
<td>Decreased BP and CO, increased HR, theoretical chance of coronary steal**&lt;sup&gt;**&lt;/sup&gt;</td>
<td>Decreased BP, CO, HR, and conduction</td>
<td>—</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.7</td>
<td>ECG seizure-like activity Increased ICP</td>
<td>Stable HR, decreased contractility</td>
<td>Sensitizes myocardium to epinephrine-induced arrhythmias</td>
<td>—</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.8</td>
<td>Increased ICP and cerebral blood flow</td>
<td>—</td>
<td>Decreased BP, CO, HR, and conduction</td>
<td>Can cause decreased HR in pediatric cases in those with existing heart disease</td>
</tr>
<tr>
<td>Nitrous oxide (N2O)*</td>
<td>104</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

*Properties and Adverse Effects of N2O

Due to its high MAC, nitrous oxide is combined with other anesthetic gases to attain surgical anesthesia. A MAC of 104% is possible in a pressurized chamber only. Second Gas Effect: see Determinants of Speed of Onset of Volatile Anesthetics sidebar, A17

Expansion of closed spaces: closed spaces such as a pneumothorax, the middle ear, bowel lumen and ET cuff will markedly enlarge if N2O is administered

Diffusion hypoxia: during anesthesia, the washout of N2O from body stores into alveoli can dilute the alveolar [O2], creating a hypoxic mixture if the original [O2] is low

**Coronary steal: isoflurane causes small vessel dilation which may compromise blood flow to areas of the heart with fixed perfusion (e.g. stents, atherosclerosis)
Table 14. Depolarizing Muscle Relaxants (Non-Competitive): Succinylcholine (SCh)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Mimics ACh and binds to ACh receptors causing prolonged depolarization; initial fasciculation may be seen, followed by temporary paralysis secondary to blocked ACh receptors by SCh.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intubating Dose</td>
<td>1-1.5 mg/kg</td>
</tr>
<tr>
<td>Onset</td>
<td>30-60 s – RAPID (fastest of all muscle relaxants)</td>
</tr>
<tr>
<td>Duration</td>
<td>3-5 min – SHORT (no reversing agent for SCh)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>SCh is hydrolyzed by plasma cholinesterase (pseudocholinesterase), found only in plasma and not at the NMJ.</td>
</tr>
</tbody>
</table>
| Indications         | • Assist intubation  
• Increased risk of aspiration (need rapid paralysis and airway control)  
• Short procedures (e.g. full stomach), hiatus hernia, obesity, pregnancy, trauma  
• Electroconvulsive therapy (ECT)  
• Laryngospasm                                                                                     |
| Side Effects         | 1. SCh also stimulates muscarinic cholinergic autonomic receptors (in addition to nicotinic receptors)                                                                                                  |
|                      | • May cause bradycardia, dysrhythmias, sinus arrest, increased secretions of salivary glands (especially in children)                                                                                   |
|                      | 2. Hyperkalemia                                                                                                                                     |
|                      | • Disruption of motor nerve activity causes proliferation of extrajunctional (outside NMJ) cholinergic receptors                                                                                       |
|                      | • Depolarization of an increased number of receptors by SCh may lead to massive release of potassium out of muscle cells                                                                               |
|                      | • Patients at risk  
• 3rd degree burns 24 h-6 mo after injury  
• Traumatic paralysis or neuromuscular diseases (e.g. muscular dystrophy)  
• Severe intra-abdominal infections  
• Severe closed head injury  
• Upper motor neuron lesions                                                                                                               |
|                      | 3. Can trigger MH                                                                                                                                    |
|                      | 4. Increased ICP/Intraocular pressure/intragastric pressure (no increased risk of aspiration if competent lower esophageal sphincter)                                                               |
|                      | 5. Fasciculations, post-operative myalgia – may be minimized if small dose of non-depolarizing agent given before SCh administration                                                                  |
| Contraindications   | Absolute  
• Known hypersensitivity or allergy, positive history of malignant hyperthermia, myotonia (m. congenita, m. dystrophica, paramyotonia congenital), high risk for hyperkalemic response |
|                      | Relative  
Known history of plasma cholinesterase deficiency, myasthenia gravis, myasthenic syndrome, familial periodic paralysis, open eye injury  

Table 15. Non-Depolarizing Muscle Relaxants (Competitive)

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Competitive blockade of postsynaptic ACh receptors preventing depolarization</th>
</tr>
</thead>
</table>
| Classification      | Mivacuronium  
Rocuronium  
Vercuronium  
Cisatracurium  
Pancuronium |
| Class               | Short  
Intermediate  
Long |
| Intubating Dose (mg/kg) | 0.2  
0.6-1.0  
0.1  
0.2  
0.1 |
| Onset (min)         | 2-3  
1.5  
2-3  
3  
3-5 |
| Duration (min)      | 15-25  
30-45  
45-60  
40-60  
90-120 |
| Metabolism          | Plasma cholinesterase  
Liver (major) Renal (minor)  
Liver  
Hofmann Eliminations  
Renal (major) Liver (minor) |
| Indications         | Assist intubation, assist mechanical ventilation in some ICU patients, reduce fasciculations and post-operative myalgias secondary to SCh |
| Side Effects         | Histamine Release  
Yes  
No  
No  
No  
No |
|                      | Other  
---  
---  
---  
---  
--- |
| Considerations      | Increased duration of action in renal or liver failure  
Quick onset of rocuronium allows its use in rapid sequence induction  
Cisatracurium is good for patients with renal or hepatic insufficiency  
Pancuronium if increased HR and BP desired |

Table 16. Reversal Agents for Non-Depolarizing Relaxants

| Cholinesterase Inhibitor | Neostigmine  
Pyridostigmine  
Edrophonium |
|--------------------------|--------------------------------------------------|
| Onset and Duration       | Intermediate  
Longest  
Shortest |
| Mechanism of Action      | Inhibits enzymatic degradation of ACh, increases ACh at nicotinic and muscarinic receptors, displaces non-depolarizing muscle relaxants |
| Muscarinic effects of reversing agents include unwanted bradycardia, salivation, and increased bowel peristalsis* |
| Dose (mg/kg)             | 0.04-0.08  
0.1-0.4  
0.5-1 |
| Recommended Anticholinergic | Glycopyrolate  
Glycopyrolate  
Atropine |
| Dose of Anticholinergic per mg | 0.2  
0.05  
0.014 |

*Atropine and glycopyrolate are anticholinergic agents administered during the administration of reversal agents to minimize muscarinic effects

Table 17. Local Anesthetic Agents

<table>
<thead>
<tr>
<th></th>
<th>Maximum Dose</th>
<th>Maximum Dose with Epinephrine</th>
<th>Potency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>chloroprocaine</td>
<td>11 mg/kg</td>
<td>14 mg/kg</td>
<td>Low</td>
<td>15-30 min</td>
</tr>
<tr>
<td>lidocaine</td>
<td>5 mg/kg</td>
<td>7 mg/kg</td>
<td>Medium</td>
<td>1-2 h</td>
</tr>
<tr>
<td>bupivacaine</td>
<td>2.5 mg/kg</td>
<td>3 mg/kg</td>
<td>High</td>
<td>3-6 h</td>
</tr>
<tr>
<td>ropivacaine</td>
<td>2.5 mg/kg</td>
<td>3 mg/kg</td>
<td>High</td>
<td>2-8 h</td>
</tr>
</tbody>
</table>
Appendices

Difficult Tracheal Intubation in Unconscious Patient

Figure 14. Difficult tracheal intubation encountered in the unconscious patient

SGD = supraglottic device

Difficult Tracheal Intubation

Airway exam or history predicts difficult tracheal intubation

If general anesthesia is induced . . .
1. Is tracheal intubation predicted to success in no more than 3 attempts?
2. If tracheal intubation fails, will face mask or SGD ventilation succeed?

. . . and are other patient and contextual issues favourable?
1. Rapid oxygen desaturation unlikely with onset of apnea?
2. Little risk of aspiration once unconscious?
3. No obstructing airway pathology?
4. Additional skilled help available?
5. Clinician skilled in planned technique(s) and equipment available?

Low risk of failed oxygenation if induced
Consider intubation after induction of general anesthesia
• e.g. IV induction (e.g. RSI)
• e.g. inhalational induction

Significant risk of failed oxygenation if induced
Consider awake intubation/techniques
• e.g. awake oral/nasal
• e.g. awake tracheotomy

Is awake intubation feasible?
• Patient can cooperate
• Situation acuity permits

Other options
• e.g. induction with “double set-up” preparation for immediate cricothyrotomy or tracheotomy

Figure 15. Anticipated difficult tracheal intubation
IV = intravenous; RSI = rapid sequence induction/intubation; SGD = supraglottic device

Figure 16. Adult cardiac arrest algorithm
**Adult Tachycardia**

**With Pulse**

1. Assess appropriateness for clinical condition
   - Heart rate typically ≥150/min if tachyarrhythmia

2. Identify and treat underlying cause
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry

3. Persistent tachyarrhythmia causing:
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. Synchronized cardioversion
   - Consider sedation
   - If regular narrow complex, consider adenosine

5. Wide QRS? ≥0.12 second
   - IV access and 12-lead ECG if available
   - Consider adenosine only if regular and monomorphic
   - Consider antiarrhythmic infusion
   - Consider expert consultation

6. Persistent tachyarrhythmia causing:
   - Adenosine IV Dose:
     - First dose: 6 mg rapid IV push; follow with NS flush
     - Second dose: 12 mg if required
   - Antiarrhythmic Infusions for Stable Wide-QRS Tachycardia
     - Procainamide IV Dose:
       - First dose: 20-50 mg/min until arrhythmia suppressed, hypotension ensues, QRS duration increases ≥50%, or maximum dose 17 mg/kg given
       - Maintenance infusion: 1-4 mg/min
       - Avoid if prolonged QT or CHF
     - Amiodarone IV Dose:
       - First dose: 150 mg over 10 min
       - Repeat as needed if VT recurs
       - Follow by maintenance infusion of 1 mg/min for first 6 h
     - Sotalol IV Dose:
       - 100 mg (1.5 mg/kg) over 5 min
       - Avoid if prolonged QT

**Adult Bradycardia**

**With Pulse**

1. Assess appropriateness for clinical condition
   - Heart rate typically <50/min if bradyarrhythmia

2. Identify and treat underlying cause
   - Maintain patent airway; assist breathing as necessary
   - Oxygen (if hypoxemic)
   - Cardiac monitor to identify rhythm; monitor blood pressure and oximetry
   - IV access
   - 12-Lead ECG if available; do not delay therapy

3. Persistent bradyarrhythmia causing:
   - Hypotension?
   - Acutely altered mental status?
   - Signs of shock?
   - Ischemic chest discomfort?
   - Acute heart failure?

4. Monitor and observe
   - No
   - Yes

5. Atropine
   - If atropine ineffective:
     - Transcutaneous pacing
     - Dopamine infusion
     - Epinephrine infusion

6. Consider:
   - Expert consultation
   - Transvenous pacing

---

**Figure 17. Adult tachycardia algorithm**


**Figure 18. Adult bradycardia algorithm**

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Acronyms

AAA abdominal aortic aneurysm
ABI ankle-brachial index
ACEI angiotensin converting enzyme inhibitor
ACS acute coronary syndrome
ABF atrial fibrillation
AR aortic regurgitation
ARB angiotensin receptor blocker
ARDS acute respiratory distress syndrome
AS aortic stenosis
ASA acetylsalicylic acid (Aspirin®)
ASD atrial septal defect
AV atrioventricular
BBB bundle branch block
BNP brain natriuretic peptide
BP blood pressure
CABG coronary artery bypass graft
CAD coronary artery disease
CCT coronary artery bypass graft
CCB calcium channel blocker
CHF congestive heart failure
CXR chest x-ray
COPD chronic obstructive pulmonary disease
CSF cerebrospinal fluid
CVD cerebrovascular disease
CXR chest x-ray
CSS cerebrovascular surgery
CT coronary tomography
CTA computed tomography angiography
CTCA computed tomography coronary angiography
CTA computed tomography angiography
DCM dilated cardiomyopathy
DDAVP desmopressin
DDAVP desmopressin acetate
DDT deep vein thrombosis
diabetes mellitus
LV left ventricle
LVEF left ventricular ejection fraction
LVMH low molecular weight heparin
MRA MRI angiography
NSTEMI non-ST elevation myocardial infarction
NSR normal sinus rhythm
OS opening snap
PCWP pulmonary capillary wedge pressure
PIF posterior inferior wall
PIVM posterior inferior wall myocardial infarction
POL posterior descending artery
PAD patellar artery
PDU peripheral digital unit
PCI percutaneous coronary intervention
PDA patent ductus arteriosus
PE pulmonary emobolism
PII posterior interventricular artery
PIV posterior interventricular vein
PIV posterior interventricular artery
PLI posterior lateral interventricular artery
PNS premature nodal supraventricular tachycardia
PNS premature nodal supraventricular tachycardia
PND point of maximal impulse
PNI point of maximal impulse
PND paroxysmal nocturnal dyspnea
PUS peptic ulcer disease
PVC premature ventricular contraction
PVD peripheral vascular disease
RA right atrium
RAO right anterior oblique
RAH right heart hypertrophy
RAO right anterior oblique
RBB right bundle branch
RBBB right bundle branch block
RVW right ventricular hypertrophy
RVW right ventricular hypertrophy
SA sinoatrial	
SAH sudden cardiac death
SEM systolic ejection murmur
SCM systemic lupus erythematosus
STEMI ST elevation myocardial infarction
SV stroke volume
SVT supraventricular tachycardia
TA thoracic aortic aneurysm
TEE transesophageal echocardiography
TB tuberculosis
TIA transient ischemic attack
TR tricuspid regurgitation
TTE transthoracic echocardiography
TVI ventricular tachycardia
WFT Wolff-Parkinson-White

Coronary Anatomy Circulation

- conventional arterial supply to the heart arises from the right and left coronary arteries, which originate from the root of the aorta
  - right coronary artery (RCA)
    - acute marginal branches
    - atrioventricular (AV) nodal artery
    - posterior interventricular artery (PIV) = posterior descending artery (PD)
  - left main coronary artery (LCA): two major branches
    - left anterior descending artery (LAD)
      - septal branches
      - diagonal branches
    - left circumflex artery (LC)
      - obtuse marginal branches
- dominance of circulation
  - right-dominant circulation: PIV and at least one posterolateral branch arise from RCA (80%)
  - left-dominant circulation: PIV and at least one posterolateral branch arise from LC (15%)
  - balanced circulation: dual supply of posteroinferior LV from RCA and LC (5%)
- the sinoatrial (SA) node is supplied by the SA nodal artery, which may arise from the RCA (60%) or LCA (40%)
- most venous blood from the heart drains into the RA through the coronary sinus, although a small amount drains through thebesian veins into all four chambers, contributing to the physiologic R-L shunt

Figure 1. Anatomy of the coronary arteries (right anterior oblique projection)
Figure 2a. Cardiac cycle
Grey shaded bars indicate isovolumic contraction (left) and isovolumic relaxation (right)

Figure 2b. JVP waveform

Legend:
AV – aortic valve
LA – left atrium
LV – left ventricle
MV – mitral valve

Cardiac Anatomy

- layers of the heart
  - endocardium
  - myocardium
  - epicardium
  - visceral pericardium
  - parietal pericardium

- valves
  - semilunar valves: no subvalvular apparatus present
    - aortic valve, 3 valve leaflets: separates LV and ascending aorta
    - pulmonic valve, 3 valve leaflets: separates RV and main pulmonary artery (PA)
  - atrioventricular valves: subvalvular apparatus present in the form of chordae tendinae and papillary muscles
    - tricuspid valve, 3 valve leaflets: separates RA and RV
    - mitral valve, 2 valve leaflets: separates LA and LV

- conduction system
  - SA node governs pacemaking control
  - anterior-, middle-, and posterior-interval nodal tracts carry impulses in the right atrium and along Bachmann's bundle in the left atrium
  - atrial impulses converge at the AV node
    - the AV node is the only conducting tract from the atria to the ventricles because of electrical isolation by the annulus fibrosis (except when accessory pathways are present)
    - the bundle of His bifurcates into left and right bundle branches (LBB and RBB)
    - RBB further splits into anterior and posterior fascicles
    - RBB and fascicles of LBB give off Purkinje fibres which conduct impulses into the ventricular myocardium

Figure 3. Conduction system of the heart

Figure 4. Blood vessel structure

Features of Abnormal JVP Wave Formation
- Atrial fibrillation: absent a wave
- 3rd degree heart block: cannon a waves
- Tricuspid regurgitation: cv wave, elevated JVP
- Cardiac tamponade: x descent only, absent y descent
- Constrictive pericarditis: prominent y descent, Kussmaul's sign (paradoxic increase in JVP with inspiration)

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cardiovascular innervation
- sympathetic nerves
  - innervate the SA node, AV node, ventricular myocardium and vasculature
  - SA node (β1) fibres increase pacemaking activity (chronotropy)
  - cardiac muscle (β1) fibres increase contractility (inotropy) to help increase cardiac output
  - stimulation of β1- and β2-receptors in the skeletal and coronary circulation causes vasodilatation
- parasympathetic nerves
  - innervate the SA node, AV node, atrial myocardium but few vascular beds
  - basal vagal tone dominates the tonic sympathetic stimulation of the SA node and AV node resulting in slowing of pacemaker activity and conduction (i.e. reduced dromotropy – if only affecting AV node conduction)
  - parasympathetics have very little impact on total peripheral vascular resistance

Differential Diagnoses of Common Presentations

Note: **bold** text indicates most common, *underlined* text indicates life threatening condition

### Chest Pain
- cardiac
  - **MI**/angina
  - myocarditis
  - pericarditis/Dressler’s syndrome
  - cardiac tamponade
- pulmonary
  - pneumonia
  - PE
  - pneumothorax/hemothorax, tension pneumothorax
  - empyema
  - pulmonary neoplasm
  - bronchiectasis
  - TB
- gastrointestinal
  - esophageal: spasm, GERD, esophagitis, ulceration, achalasia, neoplasm, Mallory-Weiss syndrome, esophageal rupture

### Loss of Consciousness
- hypovolemia
- cardiac
  - structural or obstructive causes
    - ACS
    - AS
    - HCM
    - *cardiac tamponade*, constrictive pericarditis
    - arrhythmias (see Arrhythmias, C17)
- respiratory
  - massive pulmonary embolism
  - pulmonary hypertension
  - hypoxia
  - hypercapnia
- neurologic
  - stroke/TIA
    - (esp. vertebrobasilar insufficiency)

### Generalized Edema
- increased hydrostatic pressure/fluid overload
  - heart failure
  - pregnancy
  - drugs (e.g. CCBs)
  - *iatrogenic* (e.g. IV fluids)
- decreased oncotic pressure/ hypoalbuminemia
  - nephrotic syndrome
- liver cirrhosis
- malnutrition
- increased capillary permeability
- severe sepsis
- hormonal
- hypothyroidism
- exogenous steroids
- pregnancy
- estrogens

### Local Edema
- inflammation/infection
- venous or lymphatic obstruction
  - thrombophlebitis/deep vein thrombosis
- venous insufficiency
- chronic lymphangitis
- lymphatic tumour infiltration
- filariasis
- migraine
- seizure
- metabolic
  - anemia
  - *hypoglycemia*
- drugs
  - antihypertensives
  - antiarrhythmics
  - diuretics
  - vasovagal
  - autonomic dysfunction
  - diabetic neuropathy
  - psychiatric
  - panic attack
Palpitations

- cardiac
  - arrhythmias (PAC, PVC, SVT, VT)
  - valvular heart disease
  - HCM
- endocrine
  - thyrotoxicosis
  - pheochromocytoma
  - hypoglycemia
- systemic
  - fever
  - anemia
- drugs
  - stimulants and anticholinergics
- psychiatric
  - panic attack

Dyspnea

- cardiovascular
  - acute MI
  - CHF/LV failure
  - aortic/mitral stenosis
  - aortic/mitral regurgitation
  - arrhythmia
  - cardiac tamponade
  - constrictive pericarditis
  - left-sided obstructive lesions (e.g. left atrial myxoma)
  - elevated pulmonary venous pressure
- respiratory
  - airway disease
    - asthma
  - COPD exacerbation
  - upper airway obstruction
    (anaphylaxis, foreign body, mucus plugging)
- parenchymal lung disease
  - ARDS
  - pneumonia
  - interstitial lung disease
  - pulmonary vascular disease
  - PE
  - pulmonary HTN
  - pulmonary vasculitis
  - pleural disease
  - pneumothorax
  - pleural effusion
  - neuromuscular and chest wall disorders
    - C-spine injury
    - polymyositis, myasthenia gravis, Guillain-Barré syndrome
    - kyphoscoliosis
    - anxiety/psychosomatic
    - hematological/metabolic
      - anemia, acidosis, hypercapnia

Cardiac Diagnostic Tests

Electrocardiography Basics

Description
- a graphical representation (time versus amplitude of electrical vector projection) of the electrical activity of the heart

Indications
- detect myocardial injury, ischemia, and the presence of prior infarction
- palpitations, syncope, antiarrhythmic drug monitoring
- arrhythmia surveillance in patients with documented or potentially abnormal rhythms
- surveillance of non-sustained arrhythmias that can lead to prophylactic intervention

Contraindications
- no absolute contraindications
- patient refusal
- allergies (sensitivities to electrodelatex adhesive)

Risks
- no absolute risks

on the ECG graph
  - the horizontal axis represents time (at usual paper speed 25 mm/s)
    - 1 mm (1 small square) = 40 msec
    - 5 mm (1 large square) = 200 msec
  - the vertical axis represents voltage (at usual standard gain setting 10 mm/mV)
    - 1 mm (1 small square) = 0.1 mV
    - 10 mm (2 large squares) = 1 mV
- leads
  - standard 12-lead ECG
    - limb leads: I, II, III, aVL, aVF, aVF
    - precordial leads: V1-V6 (V1-V2 septal, V3-V4 anterior, V5-V6 lateral)
  - additional leads
    - right-sided leads: V3R-V6R (useful in RV infarction and dextrocardia)
    - lateral = I, aVL, V5, V6; inferior = II, III, aVF; anterior = V1-V4

Figure 5. ECG lead placement

Figure 6. ECG waveforms and normal values
Approach to ECGs

Introduction
Historically, the electrocardiogram has been a tricky subject for medical students. For many years, the classical approach has been taught in medical schools, which has demystified the ECG. Below, we are presenting both the Classical Approach and the newer PQRSTU Approach to provide students with different ways to view the ECG. Despite methodological differences, the rigor and final result is the same. These two approaches should help you better understand the concepts of ECG interpretation and equip you with the necessary skills to interpret ECGs in exam scenarios and clinical practice.

Classical Approach to ECGs

RATE
• normal = 60-100 bpm (atrial rate: 150-250 bpm = paroxysmal tachycardia, 250-350 bpm = atrial flutter, >350 bpm = AFib)
• regular rhythm
  • to calculate the rate, divide 300 by number of large squares between 2 QRS complexes (there are 300 large squares in 1 min: 300 x 200 msec = 60 sec)
  • or remember 300-150-100-75-60-50-43 (rate falls in this sequence with the number of large squares between 2 QRS complexes)
• irregular rhythm
  • rate = 6 x number of R-R intervals in 10 s (the ”rhythm strips” are 10 sec recordings)
  • types: wandering pacemaker, multifocal atrial tachycardia, AFib
• atrial escape = 60-80 bpm; junctional escape = 40-60 bpm; ventricular escape = 20-40 bpm

RHYTHM
• regular: R-R interval is the same across the tracing
• irregular: R-R interval varies across the tracing
• regularly irregular: repeating pattern of varying R-R intervals
• irregularly irregular: R-R intervals vary erratically
• normal sinus rhythm (NSR)
  • P wave precedes each QRS; QRS follows each P wave
  • P wave axis is normal (positive in 2 out of the 3 following leads I, aVF, II)
  • rate between 60-100 bpm

AXIS
• mean axis indicates the direction of the mean vector
• can be determined for any waveform (P, QRS, T)
• the standard ECG reported QRS axis usually refers to the mean axis of the frontal plane – it indicates the mean direction of ventricular depolarization forces
• QRS axis in the frontal plane
  • normal axis: -30° to 90° (i.e. positive QRS in leads I and II)
  • left axis deviation (LAD): axis < -30°
  • right axis deviation (RAD): axis > 90°
• QRS axis in the horizontal plane is not routinely calculated – it is directed posteriorly and to the left
• transition from negative to positive is usually in lead V3

Table 1. Conduction Abnormalities

<table>
<thead>
<tr>
<th>Left Bundle Branch Block (LBBB)</th>
<th>Right Bundle Branch Block (RBBB)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete LBBB</strong></td>
<td><strong>Complete RBBB</strong></td>
</tr>
<tr>
<td>QRS duration &gt;120 msec</td>
<td>QRS duration &gt;120 msec</td>
</tr>
<tr>
<td>Broad notched R waves in leads V5, and V5, and usually I, aVL</td>
<td>Positive QRS in lead V1 (SR' or occasionally broad R wave)</td>
</tr>
<tr>
<td>Deep broad S waves in leads V1-2</td>
<td>Broad S waves in leads I, V5-6 (&gt;40 msec)</td>
</tr>
<tr>
<td>Secondary ST-T changes (+ve in leads with broad notched R waves, +ve in V1-2) are usually present</td>
<td>Usually secondary T wave inversion in leads V1-2</td>
</tr>
<tr>
<td>LBBB can mask ECG signs of MI</td>
<td>Frontal axis determination using only the first 60 msec</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Anterior Fascicular Block (LAFB) (Left Anterior Hemiblock)</th>
<th>Left Posterior Fascicular Block (LPFB) (Left Posterior Hemiblock)</th>
<th>Bifascicular Block</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Axis Deviation (-30° to -90°)</strong></td>
<td><strong>Right Axis Deviation (110° to 180°)</strong></td>
<td><strong>RBBB pattern</strong></td>
</tr>
<tr>
<td>Small q and prominent R in leads I and aVL</td>
<td>Small r and prominent S in leads I and aVL</td>
<td>Small q and prominent R</td>
</tr>
<tr>
<td>Small r and prominent S in leads II, III, and aVF</td>
<td>Small q and prominent R in leads II, III, and aVF</td>
<td>The first 60 msec (1.5 small squares) of the QRS shows the pattern of LAFB or LPFB</td>
</tr>
<tr>
<td>Bifascicular block refers to impaired conduction in two of the three fascicles, most commonly a RBBB and left anterior hemiblock; the appearance on an ECG meets the criteria for both types of blocks</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 7. Axial reference system
Each lead contains a (+) area displayed by the bold arrows. Impulses traveling toward the positive region of the lead results in an upward deflection in that lead. Normal QRS axis is between -30° and +90°.
Nonspecific Intraventricular Block
- QRS duration >120 msec
- absence of definitive criteria for LBBB or RBBB

Table 2. Hypertrophy/Chamber Enlargement

<table>
<thead>
<tr>
<th>Left Ventricular Hypertrophy (LVH)</th>
<th>Right Ventricular Hypertrophy (RVH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• S in V1 + R in V5 or V6 &gt;35 mm above age 40, (&gt;40 mm for age 31-40, &gt;45 mm for age 21-30)</td>
<td>• Right axis deviation</td>
</tr>
<tr>
<td>• R in aVL &gt;11 mm</td>
<td>• R/S ratio &gt;1 or qR in lead V1</td>
</tr>
<tr>
<td>• R in I + S in III &gt;25 mm</td>
<td>• RV strain pattern: ST segment depression and T wave inversion in leads V1-2</td>
</tr>
<tr>
<td>• Additional criteria</td>
<td>• Additional criteria</td>
</tr>
<tr>
<td>• LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
<td>• LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
</tr>
<tr>
<td>• Left atrial enlargement</td>
<td>• LV strain pattern (ST depression and T wave inversion in leads I, aVL, V4-V6)</td>
</tr>
<tr>
<td>• N.B. The more criteria present, the more likely LVH is present.</td>
<td>• N.B. The more criteria present, the more likely LVH is present.</td>
</tr>
<tr>
<td>• If only one voltage criteria present, it is called minimal voltage criteria for LVH which could be a normal variant</td>
<td>• If only one voltage criteria present, it is called minimal voltage criteria for LVH which could be a normal variant</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Left Atrial Enlargement (LAE)</th>
<th>Right Atrial Enlargement (RAE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Biphasic P wave with the negative terminal component of the P wave in lead V1 ≥1 mm wide and ≥1 mm deep</td>
<td>• P wave &gt;2.5 mm in height in leads II, III, or aVF (“P pulmonale”)</td>
</tr>
<tr>
<td>• P wave &gt;100 msec, could be notched in lead II (“P mitrale”)</td>
<td></td>
</tr>
</tbody>
</table>

ISCHEMIA/INFARCTION
- look for the anatomic distribution of the following ECG abnormalities (see Table 3)
- ischemia
  - ST segment depression
  - T wave inversion (most commonly in V1-V6)
- injury
  - transmural (involving the epicardium)
    - ST elevation in the leads facing the area injured/infarcted
    - transient ST elevation may occur in patients with coronary artery spasm (e.g. Prinzmetal angina) which can be slight or prominent (>10 mm)
  - subendocardial
    - marked ST depression in the leads facing the affected area
    - may be accompanied by enzyme changes and other signs of MI
    - may also occur with angina

Figure 10. Typical ECG changes with infarction
- evolving infarction (ST elevation in contiguous leads in the same territory = acute MI)
- ST elevation: at least 1 mm in 2 adjacent limb leads or at least 1-2 mm in adjacent precordial leads in STEMI (signifies occlusion and transmural ischemic injury) vs. diffuse pattern in early pericarditis
- "typical" sequential changes of evolving MI
  1. hyperacute T waves (tall, symmetric T waves) in the leads facing the infarcted area, with or without ST elevation
  2. ST elevation (injury pattern) in the leads facing the infarcted area
    • usually in the first hours post infarct
    • in acute posterior infarction, there is ST depression in V1-V3 (reciprocal to ST elevation in the posterior leads, that are not recorded in the standard 12-lead ECG)
  3. significant Q waves: >40 msec or >1/3 of the total QRS and present in at least 2 consecutive leads in the same territory (hours to days post-infarct)
  4. inverted T waves (one day to weeks after infarction)
    • this classical sequence does not always occur
    - Q waves of infarction may appear in the very early stages, with or without ST changes
    - non-Q wave infarction: there may be only ST or T changes despite clinical evidence of infarction
• completed infarction
  ▪ abnormal Q waves (Q waves may be present in leads III and aVL in normal individuals due to initial septal depolarization)
    ▪ duration >40 msec (>30 msec in aVF for inferior infarction)
    ▪ Q/QRS voltage ratio is >33%
    ▪ present in at least 2 consecutive leads in the same territory
  ▪ abnormal R waves (R/S ratio >1, duration >40 msec) in V1 and occasionally in V2 are found in posterior infarction (usually in association with signs of inferior and/or lateral infarction)

Table 3. Areas of Infarction/Ischemia (right dominant anatomy)

<table>
<thead>
<tr>
<th>Vessel Usually Involved</th>
<th>Infarct Area (LAD and LC)</th>
<th>Leads (LAD and LC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left anterior descending (LAD)</td>
<td>Anteroseptal</td>
<td>V1, V2</td>
</tr>
<tr>
<td></td>
<td>Anterior</td>
<td>V2, V4</td>
</tr>
<tr>
<td></td>
<td>Anterolateral</td>
<td>I, aVL, V3-6</td>
</tr>
<tr>
<td></td>
<td>Extensive anterior</td>
<td>I, aVL, V1-6</td>
</tr>
<tr>
<td>Right coronary artery (RCA)</td>
<td>Inferior</td>
<td>II, III, aVF</td>
</tr>
<tr>
<td></td>
<td>Right ventricle</td>
<td>V3R, V4R (right sided chest leads)</td>
</tr>
<tr>
<td></td>
<td>Posterior MI (assoc. with inf. MI)</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
<tr>
<td>Left circumflex (LCX)</td>
<td>Lateral</td>
<td>I, aVL, V5-6</td>
</tr>
<tr>
<td></td>
<td>Isolated posterior MI</td>
<td>V1, V2 (prominent R waves)</td>
</tr>
</tbody>
</table>

### MISCELLANEOUS ECG CHANGES

**Electrolyte Disturbances**

- hyperkalemia
  ▪ mild to moderate (K+ 5-7 mmol/L): tall peaked T waves
  ▪ severe (K+ >7 mmol/L): progressive changes whereby P waves flatten and disappear, QRS widens and may show bizarre patterns, axis shifts left or right, ST shift with tall T waves, eventually becomes a "sine wave" pattern
- hypokalemia
  ▪ ST segment depression, prolonged QT interval, low T waves, prominent U waves (U>T)
  ▪ enhances the toxic effects of digitals
- hypercalcemia
  ▪ shortened QT interval (more extracellular Ca²⁺ means shorter plateau in cardiac action potential)
- hypocalcemia
  ▪ prolonged QT interval (less extracellular Ca²⁺ means longer plateau in cardiac action potential)

**Hypothermia**

- sinus bradycardia
- when severe, prolonged QRS and QT intervals
- AFib with slow ventricular response and other atrial/ventricular dysrhythmias
- Osborne J waves: “hump-like” waves at the junction of the J point and the ST segment

**Pericarditis**

- early: diffuse ST segment elevation ± PR segment depression, upright T waves
- later: isoelectric ST segment, flat or inverted T waves
- ± tachycardia

**Drug Effects**

- digitals
  ▪ therapeutic levels may be associated with "digitalis effect"
    ▪ ST downsloping or "scooping"
    ▪ T wave depression or inversion
    ▪ QT shortening ± U waves
    ▪ slowing of ventricular rate in AFib

### Low Voltage

- Definition: total QRS height in precordial leads <10 mm and/or limb leads <5 mm
- Differential diagnosis
  ▪ Myocardial disease
    ▪ Ischemia
    ▪ Cardiomyopathy (usually infiltrative type), myocardiitis
  ▪ Pericardial effusion
  ▪ Thick chest wall/barrel chest: COPD, obesity
  ▪ Generalized edema
  ▪ Hypothyroidism/myxedema
  ▪ Inappropriate voltage standardization

**Figures**

- Figure 11. Hyperkalemia
- Figure 12. Hypokalemia
- Figure 13. Osborne J waves of a hypothermic patient
- Pacemakers
  ▪ Demand pacemaker has discharge (narrow vertical spike on ECG strip) prior to widened QRS
  ▪ Atrial pacemaker has discharge prior to P wave
  ▪ Triggered pacemaker has discharge following the P wave but prior to the widened QRS
  ▪ Atrial and ventricular pacing have discharge before the P wave and widened QRS wave
• toxic levels associated with
  • arrhythmias: paroxysmal atrial tachycardia (PAT) with conduction block, severe bradycardia in AFib, accelerated junctional rhythms, PVCs, ventricular tachycardia (see Arrhythmias, C17)
  • “regularization” of ventricular rate in AFib due to a junctional rhythm and AV dissociation
• amiodarone, quinidine, phenothiazines, tricyclic antidepressants, antipsychotics, some antihistamines, some antibiotics: prolonged QT interval, U waves

Figure 14. Atrial fibrillation, ST change due to digitalis (“digitalis effect”)

Pulmonary Disorders
• cor pulmonale (often secondary to COPD)
  • low voltage, right axis deviation (RAD), poor R wave progression in precordial leads
  • RAE and RVH with strain
• multifocal atrial tachycardia (MAT)
• massive pulmonary embolism (PE)
  • sinus tachycardia and AFib/atrial flutter are the most common arrhythmias
  • RAD, RVH with strain
• most specific sign is S1Q3T3 (S in I, Q and inverted T wave in III) but rather uncommon

Alternative PQRSTU Approach to ECGs

Note: the information seen in this alternative approach – the PQRSTU Approach – is the same as the information in the Classical Approach; it is just organized in a slightly different way based on the anatomy of the ECG

Figure 15. ECG correlations with heart activity
P WAVE
- the P wave provides a view into the atria of the heart and represents atrial contraction
- the best leads to view the P waves are II and V1
- assess the P waves for rate (based on the P-P interval relative to the R-R interval), rhythm (rounded, flutter/sawtooth, fibrillation) and axis
- lead II: the P wave should be rounded, <120 msec and <2.5 mm in height
- lead V1: the P wave is biphasic with a negative phase slightly greater than the positive phase

Common P Wave Pathology
- atrial flutter: sawtooth P wave (HINT: flip the ECG upside-down to see it better if unclear)
- atrial fibrillation: absent P wave, may have fibrillatory wave, irregular rhythm
- right atrial enlargement: tall P wave (>2.5 mm) in II or V1 (P pulmonale)
- left atrial enlargement: negative deflection >1 mm deep or >1 mm wide in V1, wide (>100 msec) notched P wave in II may be present (P mitrale)

P-R INTERVAL
- the P-R interval shows the delay between atrial and ventricular contraction that is mediated by the AV node; the magnitude of the delay is referred to as “dromotropy”
- positive dromotropy increases conduction velocity (e.g. epinephrine stimulation), negative dromotropy decreases velocity (e.g. vagal stimulation)
- P-R interval should be 120-200 msec
- long P-R interval (>200 msec)
  - heart block: first degree (fixed, prolonged P-R interval), second degree Mobitz I/Wenckebach (steadily prolonging to eventual dropped beat)
  - heart block
    - first degree: fixed, prolonged P-R interval
    - second degree Mobitz I/Wenckebach: steadily prolonging P-R interval to eventual dropped beat
    - second degree Mobitz II/Hay: fixed P-R interval with ratio of beat to dropped beat (e.g. for every 3 beats, there is one dropped beat [3:1])
    - third degree/complete: variable P-R intervals, P-P and R-R intervals individually constant but not in sync
  - atrial flutter
  - sinus bradycardia (normal to have long P-R if heart rate slow)
  - hypokalemia
  - trifascicular block
- short P-R interval (<120 msec)
  - pre-excitation syndrome (delta wave: upswooping of the P-R segment into the QRS complex indicating pre-excitation)
  - accessory pathways
  - WPW

QRS COMPLEX
- the QRS is where ventricular contraction is visualized
- rate: check the R-R interval to see if it matches the P-P interval
- amplitude: check for hypertrophy (see Table 2, C7)
- narrow width (<120 msec) QRS means that the His-Purkinje system is being used
- wide width (>120 msec) QRS means that the His-Purkinje system is being bypassed or is diseased
  - BBB, VT, ventricular hypertrophy, cardiomyopathy, WPW, ectopic ventricular beat, hyperkalemia, drugs (e.g. TCAs, antiarrhythmics)
  - Q wave: the first downward deflection of the QRS complex
    - significant Q wave: >40 msec or >33% of total QRS amplitude; indicate myocardial necrosis (new or historical)
  - R and S wave abnormalities typically show pathology in terms of BBB or intraventricular abnormalities

ST SEGMENT
- one of the more famous ECG personas mostly due to its role in detecting MI
- located between QRS complex and the T wave
  - corresponds to the completion of ventricular depolarization
  - normally at the same level as "baseline/TP segment"
- ST elevation: at least 1 mm in 2 adjacent limb leads or at least 1-2 mm in adjacent precordial leads in STEMI (signifies occlusion and transmural ischemic injury) vs. diffuse pattern in early pericarditis
- ST depression: ischemia
  - ischemia which causes ST depression can result in myocardial damage (NSTEMI)
  - lateral ST depression (leads I, aVL, V5, V6) may actually indicate a STEMI in the right heart
T WAVE
- This is the repolarization phase of the ventricles (repolarization of the atria are obscured by the QRS complex)
- Typically positive (except in aVR and V1) on ECG but normal isolated negative T waves may be present (esp. in V1 and V2)
- Pathology when T wave variation occur in consecutive leads
  - Inversion: BBB, ischemia, hypertrophy, drugs (e.g. digitalis), pulmonary embolism (lead III as part of S1Q3T3 sign)
  - Elevation: infarction (STEMI, Prinzmetal, hyperacute), hyperkalemia (wider, peaked)
  - Flattened: hypokalemia, pericarditis, drugs (e.g. digitalis), pericardial effusion
  - Variations: T wave alternans; beat-to-beat variations due to PVC overlap (R on T phenomenon which may precipitate VT or VFib)
- Appropriate T wave discordance: in BBB, T wave deflection should be opposite to that of the terminal QRS deflection (i.e. T wave negative if ends with R or R'; positive if ends with S)
- Inappropriate T wave concordance suggests ischemia or infarction

Q-T INTERVAL
- This represents the duration of ventricular depolarization and repolarization and is often difficult to interpret
- Corrected QT (QTc) is often used instead in practice to correct for the repolarization duration; QTc = QT / √RR
- Normal QTc is 360-450 msec for males and 360-460 for females
  - Increased (>450 msec for males and >460 for females): risk of Torsades de Pointes (a lethal tachyarrhythmia)
  - Decreased (<360 msec): risk of VFib
- Genetic Long QT Syndrome (often a channelopathy)
- Drugs: antibiotics, SSRIs, antipsychotics, antiarrhythmics
- Electrolytes: low Ca²⁺, low Mg²⁺, low K⁺
- Others: hypothyroidism, hyperthermia, cardiomyopathy

U WAVE
- Origin unclear but may be repolarization of Purkinje fibres or delayed/prolonged repolarization of the myocardium
- More visible at slower heart rates
- Deflection follows T wave with <25% of the amplitude
- Variations from norm could indicate pathologic conditions:
  - Prominent (>25% of T wave): electrolyte (low K⁺), drugs (digoxin, antiarrhythmics)
  - Inverted (from T wave): ischemia, volume overload

Cardiac Biomarkers
- Provide diagnostic and prognostic information in acute coronary syndromes and in heart failure

Table 4. Cardiac Enzymes

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Peak</th>
<th>Duration Elevated</th>
<th>DDx of Elevation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Troponin I</td>
<td>1-2 d</td>
<td>Up to 2 wk</td>
<td>MI, CHF, AFib, acute PE, myocarditis, chronic renal insufficiency, sepsis, hypovolemia</td>
</tr>
<tr>
<td>Troponin T</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK-MB</td>
<td>1 d</td>
<td>3 d</td>
<td>MI, myocarditis, pericarditis, muscular dystrophy, cardiac defibrillation, chronic renal insufficiency, etc.</td>
</tr>
</tbody>
</table>

- Check troponin I at presentation and 8 h later ± creatine kinase-MB (CK-MB; depends on local laboratory protocol)
- New CK-MB elevation can be used to diagnose re-infarction
- Other biomarkers of cardiac disease
  - AST and LDH also increased in MI (low specificity)
  - BNP and NT-proBNP: secreted by ventricles in response to increased end-diastolic pressure and volume
  - DDx of elevated BNP: CHF, AFib, PE, COPD exacerbation, pulmonary HTN
Ambulatory ECG

- **description**
  - extended ambulatory ECG of 24 or 48 hours or 14 or 30 days duration
  - provides a view of only two or three leads of electrocardiographic data over an extended period of time
  - permits evaluation of changing dynamic cardiac electrical phenomena that are often transient and of brief duration
  - **continuous loop**: a small, lightweight, battery operated recorder that records two or three channels of electrocardiographic data
    - patient activated event markers
    - minimum of 24–48 h
  - **implantable device**: subcutaneous monitoring device for the detection of cardiac arrhythmias
    - typically implanted in the left pectoral region and stores events when the device is activated automatically according to programmed criteria or manually with magnet application
    - can be used for months to years

- **indications**
  - evaluation of cardiac rhythm abnormalities
  - has also been used for assessing pacemaker and implantable cardioverter-defibrillator function, evidence of myocardial ischemia, late potentials, and heart rate variability

- **contraindications**
  - no absolute contraindications
  - patient refusal
  - allergies (sensitivities to latex adhesive)

- **risks**: no absolute risks

Transesophageal Echocardiography (TEE)

- **description**: ultrasound beams are directed across the chest wall to obtain images of the heart

- **indications**
  - evaluation of LVEF, wall motion abnormalities, myocardial ischemia and complications of MI
  - evaluation of chamber size, wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion
  - evaluation of unexplained hypotension, murmurs, syncope, congenital heart disease

- **contraindications**
  - limited information retrieved from patients with a thick chest wall (obesity) or overcrowded ribs (underweight) due to penetration of ultrasound waves

- **risks**: No absolute risks

**Echocardiography**

**Transthoracic Echocardiography (TTE)**

- **description**: ultrasound beams are directed across the chest wall to obtain images of the heart

- **indications**
  - evaluation of LVEF, wall motion abnormalities, myocardial ischemia and complications of MI
  - evaluation of chamber size, wall thickness, valve morphology, proximal great vessel morphology, pericardial effusion
  - evaluation of unexplained hypotension, murmurs, syncope, congenital heart disease

- **contraindications**
  - limited information retrieved from patients with a thick chest wall (obesity) or overcrowded ribs (underweight) due to penetration of ultrasound waves

- **risks**: No absolute risks

**Transoesophageal Echocardiography (TEE)**

- **description**: invasive procedure used to complement transthoracic echocardiography

- **indications**
  - evaluation for left atrial/leaflet atrial appendage thrombus in a patient with atrial fibrillation/atrial flutter to facilitate clinical decision making regarding anticoagulation, cardioversion, or ablation

- **contraindications**
  - suspected acute aortic pathology (i.e. dissection, transection, intramural hematoma)
  - suspected prosthetic valve dysfunction
  - suspected complications of endocarditis (fistula, abscess)
  - known serious esophageal pathology (e.g. esophageal stricture, bleeding esophageal varices)

- **risks**
  - serious complications are extremely rare (<1 in 5,000)
  - esophageal perforation
  - gastrointestinal bleeding
  - pharyngeal hematoma
  - methemoglobinemia (topical benzocaine and related agents used for posterior pharyngeal anesthesia)
Stress Echocardiography (SE)
- **description:** echocardiography using either exercise (treadmill or bicycle) or pharmacologic agents (dobutamine) as the stress mechanism
- **indications**
  - when ECG cannot be interpreted appropriately
  - intermediate pre-test probability with normal/equivocal exercise ECG
  - post-ACS when used to decide on potential efficacy of revascularization
  - to evaluate the clinical significance of valvular heart disease
  - evaluation of myocardial viability, dyspnea of possible cardiac origin, mitral valve disease, aortic stenosis, mitral regurgitation, pulmonary hypertension in patients with hypertrophic cardiomyopathy (for LVOT obstruction)
  - dobutamine
    - pharmacologic stress for patients who are physically unable to exercise; same indications as exercise stress echo
    - low dose dobutamine stress echo can be used to assess myocardial viability and for assessing aortic stenosis with LV systolic dysfunction
- **contraindications**
  - contraindications to exercise testing
  - contraindications to dobutamine stress echocardiography: tachyarrhythmias and systemic hypertension
  - AAA has been considered as a relative contraindication to exercise testing or dobutamine stress echocardiograph
- **risks**
  - no known adverse effects
  - dobutamine: cardiac and non-cardiac side effects can occur; VF and MI are rare

Contrast Echocardiography with Agitated Saline Contrast
- **description:** improves resolution and provides real-time assessment of intracardiac blood flow
  - conventional agent is agitated saline (contains microbubbles of air)
  - allows visualization of right heart and intracardiac shunts, most commonly patent foramen ovale (PFO) and intrapulmonary shunt
- **indications**
  - cardiac shunt (ASD, VSD, etc.)
  - extra-cardiac shunt: PDA
  - pulmonary AV fistula
  - patent foramen ovale (PFO)
  - structure identification (persistent left SVC)
  - evaluation of complex congenital heart disease
  - evaluation of TR by enhancing the Doppler signal

Contrast Echocardiography with Transpulmonary Contrast Agents
- **description:** newer contrast agents are capable of crossing the pulmonary bed and achieving left heart opacification following intravenous injection; these contrast agents improve visualization of endocardial borders and enhance evaluation of LV ejection fraction, wall motion abnormalities, and intracardiac mass
- **indications**
  - visualization of the endocardial border when ≥2 consecutive segments are not seen on non-contrast images
  - potential assessment of myocardial profusion, viability
- **contraindications**
  - known hypersensitivity to perflutren (Definity)
  - for FS069 (Optison) only, known hypersensitivity to blood, blood products, or albumin
  - fixed right to left, bi-directional or transient right to left cardiac shunts
- **risks**
  - risk of non-fatal MI and death are rare
  - ultrasound contrast agents may cause back pain, headache, urticaria, and anaphylaxis

**Stress Testing**

**EXERCISE TESTING**
- **description:** cardiovascular stress test that uses treadmill or bicycle exercise with electrocardiographic and blood pressure monitoring
- **indications**
  - patients with intermediate (10-90%) pretest probability of CAD based on age, gender, and symptoms
  - ST depression <1 mm at rest, no left bundle branch block, no digoxin or estrogen use
exercise test results stratify patients into risk groups
1. low risk patients can be treated medically without invasive testing
2. intermediate risk patients may need additional testing in the form of exercise imaging studies or cardiac catheterization
3. high risk patients should be referred for cardiac catheterization

contraindications
- acute myocardial infarction (within two days)
- unstable angina pectoris
- uncontrolled arrhythmias causing symptoms of hemodynamic compromise
- symptomatic severe valvular stenosis
- uncontrolled symptomatic heart failure
- active endocarditis or acute myocarditis or pericarditis
- acute aortic dissection
- acute pulmonary or systemic embolism
- acute non-cardiac disorders that may affect exercise performance or may be aggravated by exercise
- termination of exercise testing
  - patient’s desire to stop
  - drop in systolic blood pressure of >10 mmHg from baseline despite an increase in workload, when accompanied by other evidence of ischemia
  - moderate to severe angina
  - ST elevation (>1 mm) in leads without diagnostic Q-waves (other than V1 or aVR)
  - increasing nervous system symptoms (e.g. ataxia, dizziness, or near syncope)
  - signs of poor perfusion (cyanosis or pallor)
  - technical difficulties in monitoring ECG or systolic blood pressure
  - sustained ventricular tachycardia

risks: death, myocardial infarction, arrhythmia, hemodynamic instability, and orthopedic injury (<1-5/10,000 supervised tests)

NUCLEAR CARDIOLOGY
description
- myocardial perfusion imaging (MPI) with ECG-gated single photon emission computed tomography (SPECT), using radiolabelled tracer
- evaluates myocardial viability, detects ischemia, and assesses perfusion and LV function simultaneously
- predicts the likelihood of further cardiac event rates independent of the patient’s history, examination, resting ECG, and stress ECG
- often denoted as MIBI scan with reference to radiolabelled tracer (sestamibi)
- stress with either treadmill or IV vasodilator stress (dipyridamole, adenosine, regadenoson)
- images of the heart obtained during stress and at rest 3-4 h later
- tracers
  - Thallium-201 (²⁰¹Tl, a K⁺ analogue)
  - Technetium-99 (⁹⁹Tc)-labeled tracer (sestamibi/Cardiolite® or hexamibi/Myoview®)

Indications
- exercise MPI
  - when ECG cannot be interpreted appropriately
  - intermediate pre-test probability with normal-equivocal exercise ECG
  - in patients with previous imaging whose symptoms have changed
  - to diagnose ischemia
- dipyridamole/adenosine MPI
  - to diagnose CAD in possible ACS patients with non-diagnostic ECG and negative serum biomarkers
  - when ECG is cannot be interpreted appropriately due to LBBB or V-paced rhythm among patients unable to exercise, with the same indications as exercise MPI

contraindications
- contraindications to exercise testing
- vasodilators (i.e. adenosine, regadenoson, and dipyridamole) are contraindicated in patients with hypotension, sick sinus syndrome, high-degree AV block (in the absence of backup pacemaker capability), and reactive airways disease
- pregnancy

risks: radiation exposure

STRESS ECHOCARDIOGRAPHY
- see Echocardiography, C12
Right Heart Catheterization (Swan-Ganz Catheter)

- **description:** also known as pulmonary artery catheterization
  - obtain direct measurements of central venous, right-sided intracardiac, pulmonary artery, and pulmonary artery occlusion pressures
  - can estimate cardiac output, systemic and pulmonary vascular resistance as well as mixed venous oxyhemoglobin saturation, oxygen delivery, and oxygen uptake
  - right atrial, right ventricular, and pulmonary artery pressures are recorded
  - can also be used to measure the Cardiac Index (CI)
    - \( CI = \frac{CO}{\text{body surface area}} \)
    - cardiac index is a measure of cardiac function
    - <1.8 L/min/m² usually means cardiogenic shock
    - 2.6-4.2 L/min/m² is considered normal
  - pulmonary capillary wedge pressure (PCWP)
    - obtained by advancing the catheter to wedge in the distal pulmonary artery
    - records pressure measured from the pulmonary venous system
    - in the absence of pulmonary venous disease reflects left atrial pressure

- **indications**
  - unexplained or unknown volume status in shock
  - severe cardiogenic shock (e.g. acute valvular disease, suspected pericardial tamponade)
  - suspected or known pulmonary artery hypertension
  - severe underlying cardiopulmonary disease (e.g. congenital heart disease, left-to-right shunt, severe valvular disease, pulmonary hypertension) and undergoing corrective or other surgery

- **contraindications**
  - lack of consent
  - infection at the insertion site
  - the presence of a right ventricular assist device
  - insertion during cardiopulmonary bypass

- **risks**
  - complications for diagnostic catheterization <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - complications of insertion: atrial and/or ventricular arrhythmias (~3% of patients)
  - catheter misplacement or knotting (uncommon)
  - perforation of a cardiac chamber and rupture of a cardiac valve or the pulmonary artery (rare)
  - complications of catheterization: pulmonary artery rupture, pulmonary infarction, thromboembolic events, infection, and data misinterpretation
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)
Left Heart Catheterization

- **description**
  - accomplished by introducing a catheter into the brachial or femoral artery and advancing it through the aorta, across the aortic valve, and into the left ventricle
  - evaluates mitral and aortic valvular defects and myocardial disease
  - systolic and end-diastolic pressure tracings recorded
  - LV size, wall motion and ejection fraction can be assessed by injecting contrast into the LV (left ventriculography) via femoral/radial artery catheterization
  - cardiac output (measured by the Fick oxygen method or the indicator dilution method)

- **indications**
  - identification of the extent and severity of CAD and evaluation of left ventricular function
  - assessment of the severity of valvular or myocardial disorders (e.g. aortic stenosis or insufficiency, mitral stenosis or insufficiency, and various cardiomyopathies) to determine the need for surgical correction
  - collection of data to confirm and complement noninvasive studies
  - determination of the presence of CAD in patients with confusing clinical presentations or chest pain of uncertain origin

- **contraindications**
  - severe uncontrolled hypertension
  - ventricular arrhythmias
  - acute stroke
  - severe anemia
  - active gastrointestinal bleeding
  - allergy to radiographic contrast
  - acute renal failure
  - uncontrolled congestive failure (so that the patient cannot lie flat)
  - unexplained febrile illness or untreated active infection
  - electrolyte abnormalities (e.g. hypokalemia)
  - severe coagulopathy

- **risks**
  - complications for diagnostic catheterization <1%
  - inadequate diagnostic procedures occur in <1% of cases
  - within 24 h of catheterization: death, MI, or stroke (0.2% to 0.3% of patients)

Coronary Angiography

- **description**
  - radiographic visualization of the coronary vessels after injection of radiopaque contrast media
  - coronary vasculature accessed via the coronary ostia

- **indications**
  - to define the coronary anatomy and the degree of luminal obstruction of the coronary arteries
  - to determine the presence and extent of obstructive CAD
  - to assess the feasibility and appropriateness of various forms of therapy, such as revascularization by percutaneous or surgical interventions
  - can also be used when the diagnosis of CAD is uncertain and CAD cannot be reasonably excluded by noninvasive techniques

- **contraindications**: severe renal failure (due to contrast agent toxicity – must check patient’s renal status)

- **risks**: major complications <2%, but increased in patients with pre-existing renal failure (especially in diabetic patients)

**ACC/AHA 2011 Recommended Indications for Coronary Angiography**

- Disabling (CCS classes III and IV) chronic stable angina despite medical therapy
- High-risk criteria on clinical assessment or non-invasive testing
- Serious ventricular arrhythmia or CHF
- Uncertain diagnosis or prognosis after non-invasive testing
- Inability to undergo non-invasive testing

**Coronary Angiography**

Gold standard for localizing and quantifying CAD

Hemodynamically significant stenosis is defined as 70% or more narrowing of the luminal diameter

---

**Figure 18. Coronary angiogram schematic**

AM = acute marginal; LAD = left anterior descending; OM = obtuse marginal; RCA = right coronary artery

<table>
<thead>
<tr>
<th>Chambers</th>
<th>Pressure (systolic; mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right atrium/central venous</td>
<td>1-8</td>
</tr>
<tr>
<td>Right ventricle</td>
<td>1-8 (15-30)</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>1-8 (15-30)</td>
</tr>
<tr>
<td>Left atrium/pulmonary capillary wedge</td>
<td>4-12</td>
</tr>
<tr>
<td>Left ventricle end-diastolic</td>
<td>4-12</td>
</tr>
</tbody>
</table>
Diagnostic Catheterization
• complications for diagnostic catheterization <1%
• inadequate diagnostic procedures occur in fewer than 1% of cases
• provocative pharmacological agents can be used to unmask pathology
  ▪ fluid loading may unmask latent pericardial constriction
  ▪ afterload reduction or inotropic stimulation may be used to increase the outflow tract gradient in HCM
  ▪ coronary vasoreactive agents (e.g. methylergonovine, acetylcholine)
  ▪ a variety of pulmonary vasoreactive agents in primary pulmonary HTN (e.g. oxygen, calcium channel blockers, adenosine, nitric oxide, or prostacyclin)

Contrast-Enhanced CT Coronary Angiography
• description: fast ECG-synchronized multi-slice CT image acquisition in the heart to enable non-invasive imaging of the coronary arterial tree
• indications: often used to assess coronary artery and previous graft stenosis/viability that could not be seen during coronary angiography
• sensitivity = 85%, specificity = 90% for the diagnosis of obstructive coronary disease with >50% stenosis
• contraindications: allergy to contrast dye; severe renal dysfunction
• risks: radiation exposure

Magnetic Resonance Imaging
• description: offers high spatial resolution, eliminates the need for iodinated contrast, and does not involve exposure to ionizing radiation
• indications: valuable in assessment of congenital cardiac anomalies, abnormalities of the aorta, and assessment of viable myocardium
• contraindications: metallic foreign bodies/implants
• risks: hazards posed by certain metallic devices inside patients

CARDIAC DISEASE

Arrhythmias

Mechanisms of Arrhythmias

Alterations in Impulse Formation

A. Abnormal Automaticity
• automaticity is a property of certain cardiomyocytes to spontaneously depolarize to their threshold voltage to generate action potentials in a rhythmic fashion
• under normal circumstances only cells in the specialized conduction system (SA node, AV node, and ventricular conduction system) exhibit natural automaticity. These cells are pacemaking cells. The automaticity of these cells can become abnormally increased or decreased
• in disease (e.g. post-MI ventricular ischemia) cells in the myocardium outside the conduction system may inappropriately acquire the property of automaticity and contribute to abnormal depolarization. If these ectopic generators depolarize at a rate greater than the SA node, they assume pacemaking control and become the source of abnormal rhythm
• automaticity can be influenced by:
  ▪ neurohormonal tone (sympathetic and parasympathetic stimulation)
  ▪ abnormal metabolic conditions (hypoxia, acidosis, hypothermia)
  ▪ electrolyte abnormalities
  ▪ drugs (e.g. digitalis)
  ▪ local ischemia/infarction
  ▪ other cardiac pathology
• this mechanism is responsible for the accelerated idioventricular rhythm and ventricular tachycardia that often occurs 24-72 h post MI
B. Triggered Activity due to Afterdepolarizations

1. Early Afterdepolarizations
   - occur in the context of action potential prolongation
   - consequence of the membrane potential becoming more positive during repolarization (e.g. not returning to baseline)
   - result in self-maintaining depolarizing oscillations of action potential, generating a tachyarrrhythmia (e.g. new baseline voltage is greater than threshold, which automatically triggers a new action potential after the refractory period ends)
   - basis for the degeneration of QT prolongation, either congenital or acquired, into Torsades de Pointes

2. Delayed Afterdepolarizations
   - occur after the action potential has fully repolarized, but before the next usual action potential, thus called a delayed afterdepolarization
   - commonly occurs in situations of high intracellular calcium (e.g. digitalis intoxication, ischemia) or during enhanced catecholamine stimulation (e.g. “twitchy” pacemaker cells)

Alterations in Impulse Conduction

A. Re-Entry Circuits
   - the presence of self-sustaining re-entry circuit causes rapid repeated depolarizations in a region of myocardium (see Figure 26, C22, for an example in the context of AV nodal re-entrant tachycardia)
     - e.g. myocardium that is infarcted/ischemic will consist of non-excitable and partially excitable zones which will promote the formation of re-entry circuits

B. Conduction Block
   - ischemia, fibrosis, trauma, and drugs can cause transient, permanent, unidirectional or bidirectional block
   - most common cause of block is due to refractory myocardium (cardiomyocytes are in refractory period or zone of myocardium unexcitable due to fibrosis)
   - if block occurs along the specialized conduction system distal zones of the conduction system can assume pacemaking control
   - conduction block can lead to bradycardia or tachycardia when impaired conduction leads to re-entry phenomenon

C. Bypass Tracts
   - normally the only conducting tract from the atria to the ventricles is the AV node into the His-Purkinje system
   - congenital/acquired accessory conducting tracts bypass the AV node and facilitate premature ventricular activation before normal AV node conduction
   - see Pre-Excitation Syndromes, C23

<table>
<thead>
<tr>
<th>Arrhythmias</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bradyarrhythmias (&lt;60 bpm)</strong></td>
</tr>
<tr>
<td>• Sinus bradycardia</td>
</tr>
<tr>
<td>• Sinoatrial block</td>
</tr>
<tr>
<td>• Sinus arrest</td>
</tr>
<tr>
<td>• AV block (2nd and 3rd degree)</td>
</tr>
<tr>
<td>• Junctional rhythm</td>
</tr>
<tr>
<td>• Idioventricular rhythm</td>
</tr>
<tr>
<td><strong>Tachyarrhythmias (&gt;100 bpm)</strong></td>
</tr>
<tr>
<td><strong>Regular</strong></td>
</tr>
<tr>
<td>• Narrow QRS (SVTs)</td>
</tr>
<tr>
<td>• Sinus tachycardia</td>
</tr>
<tr>
<td>• Atrial tachycardia</td>
</tr>
<tr>
<td>• Junctional tachycardia</td>
</tr>
<tr>
<td>• AVNRT</td>
</tr>
<tr>
<td>• AVRT (orthodromic)</td>
</tr>
<tr>
<td>• Atrial flutter</td>
</tr>
<tr>
<td>• Wide QRS</td>
</tr>
<tr>
<td>• SVT with aberrancy/BBB</td>
</tr>
<tr>
<td>• Ventricular tachycardia</td>
</tr>
<tr>
<td>• AVRT (antidromic)</td>
</tr>
<tr>
<td><strong>Irregular</strong></td>
</tr>
<tr>
<td>• Narrow QRS (SVTs)</td>
</tr>
<tr>
<td>• Atrial fibrillation</td>
</tr>
<tr>
<td>• A. flutter with variable block</td>
</tr>
<tr>
<td>• Multifocal atrial tachycardia</td>
</tr>
<tr>
<td>• Premature atrial contraction</td>
</tr>
<tr>
<td>• Wide QRS</td>
</tr>
<tr>
<td>• Atrial fibrillation with BBB</td>
</tr>
<tr>
<td>• A. flutter with BBB and variable block</td>
</tr>
<tr>
<td>• Polymorphic VT (torsades)</td>
</tr>
<tr>
<td>• Premature ventricular contraction</td>
</tr>
</tbody>
</table>

Figure 19. Clinical approach to arrhythmias
Bradyarrhythmias

1. SA NODAL DYSFUNCTION
A. A. Sinus Bradycardia

- P axis normal (P waves positive in I and aVF)
- Rate <60 bpm; marked sinus bradycardia (<50 bpm)
- May be seen in normal adults, particularly athletes, and in elderly individuals
- Increased vagal tone or vagal stimulation; drugs (β-blockers, calcium channel blockers, etc.); ischemia/infarction

Atropine; pacing for sick sinus syndrome

Figure 20. Sinus bradycardia

2. AV CONDUCTION BLOCKS
A. First Degree AV Block

- Prolonged PR interval (>200 msec)
- Frequently found among otherwise healthy adults

No treatment required

Figure 21. First degree AV block

B. Second Degree AV Block: Type I (Mobitz I)

- A gradual prolongation of the PR interval precedes the failure of conduction of a P wave (Wenckebach phenomenon)
- AV block is usually in AV node (proximal) triggers (usually reversible): increased vagal tone (e.g. following surgery), RCA-mediated ischemia

Figure 22. Second degree AV block with Wenckebach phenomenon (Mobitz I) (4:3 conduction) (lead V1)

B. Second Degree AV Block: Type II (Mobitz II)

- The PR interval is constant; there is an abrupt failure of conduction of a P wave
- AV block is usually distal to the AV node (i.e. bundle of His); increased risk of high grade or 3rd degree AV block

Figure 23. Second degree AV block (Mobitz II) (3:2 conduction) (lead V1)

B. Third Degree AV Block: Type II

- Complete failure of conduction of the supraventricular impulses to the ventricles; ventricular depolarization initiated by an escape pacemaker distal to the block
- Wide or narrow QRS, P-P and R-R intervals are constant, variable PR intervals; no relationship between P waves and QRS complexes (P waves “marching through”)

Management (see Electrical Pacing, C25)

Figure 24. Third degree AV block (complete heart block) (lead II)

Supraventricular Tachyarrhythmias

Presentation for SVT (and Pre-Excitation Syndromes)

- presentation can include: palpitations, dizziness, dyspnea, chest discomfort, presyncope/syncope
- may precipitate CHF, hypotension, or ischemia in patients with underlying disease
- untreated tachycardias can cause cardiomyopathy (rare, potentially reversible with treatment of SVTs)
- includes supraventricular and ventricular rhythms

Supraventricular Tachyarrhythmias

- tachyarrhythmias that originate in the atria or AV junction
- this term is used when a more specific diagnosis of mechanism and site of origin cannot be made
- characterized by narrow QRS, unless there is pre-existing bundle branch block or aberrant ventricular conduction (abnormal conduction due to a change in cycle length)

Sinus Tachycardia

- sinus rhythm with rate >100 bpm
- occurs in normal subjects with increased sympathetic tone (e.g. exercise, emotions, pain), alcohol use, caffeinated beverages, drugs (e.g. β-adrenergic agonists, anticholinergic drugs, etc.)
- etiology: fever, hypotension, hypovolemia, anemia, thyrotoxicosis, CHF, MI, shock, PE, etc.
- treatment: treat underlying disease; consider β-blocker if symptomatic, calcium channel blocker if β-blockers contraindicated
Premature Beats

- premature atrial contraction
  - ectopic supraventricular beat originating in the atria
  - P wave morphology of the PAC usually differs from that of a normal sinus beat
- junctional premature beat
  - ectopic supraventricular beat that originates in the vicinity of the AV node
  - P wave is usually not seen or an inverted P wave is seen and may be before or closely follow the QRS complex (referred to as a retrograde, or “traveling backward” P wave)
- treatment usually not required

Atrial Flutter

- rapid, regular atrial depolarization from a macro re-entrant circuit within the atrium (most commonly the right atrium)
- atrial rate 250-350 bpm, usually 300 bpm
- AV block usually occurs; it may be fixed (2:1, 3:1, 4:1, etc.) or variable
- etiology: CAD, thyrotoxicosis, mitral valve disease, cardiac surgery, COPD, PE, pericarditis
- ECG: sawtooth flutter waves (most common type of flutter) in inferior leads (II, III, aVF); narrow QRS (unless aberrancy); commonly see HR of 150
- in atrial flutter with 2:1 block, carotid sinus massage (first check for bruits), Valsalva maneuver, or adenosine may decrease AV conduction and bring out flutter waves
- treatment of acute atrial flutter
  - acute and if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if unstable (e.g. hypotension, CHF, angina): electrical cardioversion
  - if stable
    1. rate control: β-blocker, diltiazem, verapamil, or digoxin
    2. chemical cardioversion: sotalol, amiodarone, type I antiarrhythmics, or electrical cardioversion
- anticoagulation guidelines same as for patients with AFib
- treatment of long-term atrial flutter: antiarrhythmics, catheter radiofrequency (RF) ablation (success rate dependent on site of origin of atrial flutter – i.e. whether right-sided isthmus-dependent or left-sided origin)

Multifocal Atrial Tachycardia (MAT)

- irregular rhythm caused by presence of 3 or more atrial foci (may mimic AFib)
- atrial rate 100-200 bpm – 3 or more distinct P wave morphologies and PR intervals vary, some P waves may not be conducted
- occurs more commonly in patients with COPD, and hypoxemia; less commonly in patients with hypokalemia, hypomagnesemia, sepsis, theophylline, or digitalis toxicity
- treatment: treat the underlying cause; calcium channel blockers may be used (e.g. diltiazem, verapamil), β-blockers may be contraindicated because of severe pulmonary disease
- no role for electrical cardioversion, antiarrhythmics, or ablation

Atrial Fibrillation

- see CCS Atrial Fibrillation Guidelines 2014 for details (free mobile app – iCCS available on iOS and Android)
- most common sustained arrhythmia
- incidence increases with age (10% of population >80 yr old)
- symptoms: palpitations, fatigue, syncope, may precipitate or worsen heart failure
- classification
  - chronic/permanent: continuous AFib that is unresponsive to cardioversion; cardioversion should not be reattempted
  - lone: occurs in persons younger than 60 yr and in whom no clinical or echocardiographic causes are found
  - nonvalvular: not caused by valvular disease, prosthetic heart valves, or valve repair
  - paroxysmal: episodes that terminate spontaneously
  - persistent: AFib sustained for more than 7 d or AFib that terminates only with cardioversion
  - recurrent: two or more episodes of AFib
  - secondary: caused by a separate underlying condition or event (e.g. myocardial infarction, cardiac surgery, pulmonary disease, hyperthyroidism)
  - may be associated with thromboembolic events (stroke risk can be assessed by CHADS2 score in nonvalvular AFib)
- initiation
  - single circuit re-entry and/or ectopic foci act as aberrant generators producing atrial tachycardia (350-600 bpm)
  - impulses conduct irregularly across the atrial myocardium to give rise to fibrillation
  - in some cases, ectopic foci have also been mapped to the pulmonary vein ostia and can be ablated

Figure 25. Atrial flutter with variable block

Atrial Fibrillation – AFFIRM Trial
NEJM 2002;347:1825-1833
Study: Randomized, multicentre trial with mean follow-up of 3.5 yr.
Population: 4,060 patients (mean age 70 yr, 61% male, 89% white) with AF and a high risk of stroke or death.
Intervention: Rate control (β-blockers, calcium channel blockers, or digoxin alone or in combination) vs. rhythm control (antithyrrhythmic drug chosen by the treating physician).
Primary Outcome: All cause mortality.
Results: There was no difference in mortality or disabling stroke, anoxic encephalopathy, major bleeding, and cardiac arrest between the two groups. There were more incidents of hospitalizations (0.1% vs. 7%, p<0.001) and adverse events (Torsades de Pointes (12 vs. 2, p=0.007), pulseless or bradycardic arrest (9 vs. 1, p=0.01), pulmonary event (108 vs. 24, p<0.001), gastrointestinal event (117 vs. 35, p<0.001), prolonged QT interval (51 vs 4, p<0.001), bradycardia (105 vs. 64, p=0.001) in the rhythm-control group.
Conclusion: Rate-control was as effective as rhythm-control in AF and was better tolerated. There were more hospitalization incidents in the rhythm-control group.
Maintenance
- The tachycardia causes atrial structural and electrophysiological remodelling changes that further promote Afib; the longer the patient is in Afib the more difficult it is to convert back to sinus rhythm

Consequences
- The AV node irregularly filters incoming atrial impulses producing an irregular ventricular response of <200 bpm and the tachycardia leads to suboptimal cardiac output
- Fibrillatory conduction of the atria promotes blood stasis increasing the risk of thrombus formation – Afib is an important risk factor for stroke

Wide QRS complexes due to aberrancy may occur following a long-short cycle sequence if: 
- No organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic Afib on ECG
- Irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- Wide QRS complexes due to aberrancy may occur following a long-short cycle sequence (‘Ashman phenomenon’)
- Loss of atrial contraction, thus no “a” wave seen in JVP, no S4 on auscultation

Table 5. CHADS2 Risk Prediction for Non-Valvular Afib and Refer to AHA/ACC/HRS Afib Guidelines 2014 for more details

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS2 Score</th>
<th>Stroke Risk (%/Yr)</th>
<th>Anticoagulation Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive Heart Failure</td>
<td>1</td>
<td>0</td>
<td>1.9 (low)</td>
<td>ASA 81-325 mg OD</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>1</td>
<td>2.8 (low-mod)</td>
<td>Oral anticoagulants*</td>
</tr>
<tr>
<td>Age &gt; 75</td>
<td>2-3</td>
<td>2-3-4.0-5.9 (mod)</td>
<td>Oral anticoagulants*</td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>4-6</td>
<td>8.5-18.2 (high)</td>
<td>Oral anticoagulants*</td>
</tr>
<tr>
<td>Stroke/TIA (prior)</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

AFib on ECG
- No organized P waves due to rapid atrial activity (350-600 bpm) causing a chaotic fibrillatory baseline
- Irregularly irregular ventricular response (typically 100-180 bpm), narrow QRS (unless aberrancy or previous BBB)
- Wide QRS complexes due to aberrancy may occur following a long-short cycle sequence (“Ashman phenomenon”)
- Loss of atrial contraction, thus no “a” wave seen in JVP, no S4 on auscultation

Management (adapted from CCS Atrial Fibrillation Guidelines 2012 & 2014)

1. Rate control: β-blockers, diltiazem, verapamil (in patients with heart failure: digoxin, amiodarone)
2. Anticoagulation: use either warfarin or direct oral anticoagulant (DOACs) e.g. apixaban, dabigatran, rivaroxaban to prevent thromboembolism
3. Cardioversion (electrical)
   - If Afib <24-48 h, can usually cardiovert without anticoagulation
   - If Afib >24-48 h, anticoagulate for 3 wk prior and 4 wk after cardioversion due to risk of unstable intra-atrial thrombus
   - If patient unstable (hypotensive, active angina due to tachycardia, uncontrolled heart failure) should cardiovert immediately
4. Etiology
   - HTN, CAD, valvular disease, pericarditis, cardiomyopathy, myocarditis, ASD, post-operative, PE, COPD, thyrotoxicosis, sick sinus syndrome, alcohol (“holiday heart”)
   - May present in young patients without demonstrable disease (“lone Afib”) and in the elderly without underlying heart disease

Additional Management Points Regarding Afib
- Studies of patients with Afib suggest that there is no difference in long-term survival when treating patients with a rhythm-control versus rate-control strategy
- However, many patients with a significant underlying structural heart lesion (e.g. valve disease, cardiomyopathy) will not tolerate Afib well (since may be dependent on atrial kick) and these patients should be cardioverted (chemical or electrical) as soon as possible
Newly Discovered AFib
- anticoagulants may be beneficial if high risk for stroke
- if the episode is self-limited and not associated with severe symptoms, no need for antiarrhythmic drugs
- if AFib persists, 2 options
  1. rate control and anticoagulation (as indicated above)
  2. cardioversion (as above)

Recurrent AFib/Permanent AFib
- if episodes are brief or minimally symptomatic, antiarrhythmic drugs may be avoided; rate control and anticoagulation are appropriate
- patients who have undergone at least one attempt to restore sinus rhythm may remain in AFib after recurrence; permanent AFib may be accepted (with rate control and antithrombotics as indicated by CHADS2 score) in certain clinical situations
- if symptoms are bothersome or episodes are prolonged, antiarrhythmic drugs should be used
  - no or minimal heart disease: flecainide, propafenone, or sotalol
  - LV dysfunction: amiodarone
  - CAD: β-blockers, amiodarone

AV Nodal Re-Entrant Tachycardia (AVNRT)
- re-entrant circuit using dual pathways (fast conducting β-fibres and slow conducting α-fibres) within or near the AV node; often found in the absence of structural heart disease – cause is commonly idiopathic, although familial AVNRT has been reported
- sudden onset and offset
- fast regular rhythm: rate 150-250 bpm
- usually initiated by a supraventricular or ventricular premature beat
- AVNRT accounts for 60-70% of all paroxysmal SVTs
- retrograde P waves may be seen but are usually lost in the QRS complex (see Figure 27)
- treatment
  - acute: Valsalva or carotid massage, adenosine is first choice if unresponsive to vagal maneuvers; if no response, try metoprolol, digoxin, diltiazem, electrical cardioversion if patient hemodynamically unstable (hypotension, angina, or CHF)
  - long-term: 1st line – β-blocker, diltiazem, digoxin; 2nd line – flecainide, propafenone; 3rd line – catheter ablation

Figure 27. AVNRT

Figure 28. Mechanism for AVNRT

Figure 29. Accessory pathway conduction in WPW. Early ventricular activation leads to the appearance of a delta wave (slurred upstroke of the QRS) on the ECG before usual conduction across the AV node
Pre-Excitation Syndromes

• refers to a subset of SVTs mediated by an accessory pathway which can lead to ventricular pre-excitation

Wolff-Parkinson-White Syndrome
• congenital defect present in 1.5-2/1,000 of the general population
• an accessory conduction tract (Bundle of Kent; can be in right or left atrium) abnormally allows early electrical activation of part of one ventricle
• impulses travel at a greater conduction velocity across the Bundle of Kent thereby effectively "bypassing" AV node
• since the ventricles are activated earlier, the ECG shows early ventricular depolarization in the form of initial slurring of the QRS complex – the so-called "delta wave"
• atrial impulses that conduct to the ventricles through both the Bundle of Kent and the normal AV node/His-Purkinje system generate a broad “fusion complex”
• ECG features of WPW
  - PR interval <120 msec
  - delta wave: slurred upstroke of the QRS (the leads with the delta wave vary with site of bypass)
  - widening of the QRS complex due to premature activation
  - secondary ST segment and T wave changes
  - tachyarrhythmias may occur – most often AVRT and Afib

Afib in WPW Patients
• Afib is the index arrhythmia in up to 20% of patients with WPW syndrome
  - it is usually intermittent rather than persistent or permanent
• rapid atrial depolarizations in Afib are conducted through the bypass tract which is not able to filter impulses like the AV node can
• consequently the ventricular rate becomes extremely rapid (>200 bpm) and the QRS complex widens
• treatment: electrical cardioversion, IV procainamide, or IV amiodarone
  - do not use drugs that slow AV node conduction (digoxin, β-blockers) as this may cause preferential conduction through the bypass tract and precipitate VF
  - long-term: ablation of bypass tract if possible

AV Re-Entrant Tachycardia
• re-entrant loop via accessory pathway and normal conduction system
• initiated by a premature atrial or ventricular complex
• orthodromic AVRT: stimulus from a premature complex travels up the bypass tract (V to A) and down the AV node (A to V) with narrow QRS complex (no delta wave because stimulus travels through normal conduction system)
• comprises 95% of the reentrant tachycardias associated with WPW syndrome
• antidromic AVRT: more rarely the stimulus goes up the AV node (V to A) and down the bypass tract (A to V); wide and abnormal QRS as ventricular activation is only via the bypass tract
• treatment
  - acute: similar to AVNRT except avoid long-acting AV nodal blockers (e.g. digoxin and verapamil)
  - long-term: for recurrent arrhythmias ablation of the bypass tract is recommended
    - drugs such as flecainide and procainamide can be used

Ventricular Tachyarrhythmias

Premature Ventricular Contraction (PVC) or Ventricular Premature Beat (VPB)
• QRS width >120 msec, no preceding P wave, bizarre QRS morphology
• origin: LBBB morphology of VT = RV origin; RBBB morphology of VT = LV origin
• PVCs may be benign but are usually significant in the following situations
  - consecutive (≥3 = VT) or multiform (varied origin)
  - PVC falling on the T wave of the previous beat (“R on T phenomenon”): may precipitate ventricular tachycardia or VF

Accelerated Idioventricular Rhythm
• ectopic ventricular rhythm with rate 50-100 bpm
• more frequently occurs in the presence of sinus bradycardia and is easily overdriven by a faster supraventricular rhythm
• frequently occurs in patients with acute MI or other types of heart disease (cardiomyopathy, hypertensive, valvular) but it does not affect prognosis and does not usually require treatment
Ventricular Tachycardia (VT)

- 3 or more consecutive ectopic ventricular complexes
  - rate >100 bpm (usually 140-200)
  - ventricular flutter: if rate >200 bpm and complexes resemble a sinusoidal pattern
  - "sustained VT" if it lasts longer than 30 s
- ECG characteristics: wide regular QRS tachycardia (QRS usually >140 msec)
- AV dissociation; bizarre QRS pattern
- also favour Dx of VT: left axis or right axis deviation, nonspecific intraventricular block pattern, monophasic or biphasic QRS in V1 with RBBB, QRS concordance in V1-V6
- occasionally during VT supraventricular impulses may be conducted to the ventricles generating QRS complexes with normal or aberrant supraventricular morphology ("ventricular capture") or summation pattern ("fusion complexes")

- monomorphic VT
  - identical complexes with uniform morphology
  - more common than polymorphic VT
  - typically result from intraventricular re-entry circuit
  - potential causes: chronic infarct scarring, acute MI/ischemia, cardiomyopathies, myocarditis, arrhythmogenic right ventricular dysplasia, idiopathic, drugs (e.g. cocaine), electrolyte disturbances

- polymorphic VT
  - complexes with constantly changing morphology, amplitude, and polarity
  - more frequently associated with hemodynamic instability due to faster rates (typically 200-250 bpm) vs. monomorphic VT
  - potential causes: acute MI, severe or silent ischemia, and predisposing factors for QT prolongation

- treatment
  - sustained VT (>30 s) is an emergency, requiring immediate treatment
  - hemodynamic compromise: electrical cardioversion
  - no hemodynamic compromise: electrical cardioversion, lidocaine, amiodarone, type Ia agents (procaainamide, quinidine)

Figure 32. Ventricular tachycardia (monomorphic)

Table 6. Wide Complex Tachycardia: Clues for Differentiating VT vs. SVT with Aberrancy*

<table>
<thead>
<tr>
<th>Clinical Clues</th>
<th>ECG Clues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presenting symptoms</td>
<td>AV dissociation</td>
</tr>
<tr>
<td>History of CAD and previous MI</td>
<td>Capture or fusion beats</td>
</tr>
<tr>
<td>Physical exam</td>
<td>QRS width &gt;140 msec</td>
</tr>
<tr>
<td>Cannon &quot;a&quot; waves</td>
<td>Extreme axis deviation</td>
</tr>
<tr>
<td>Variable S1</td>
<td>(left or right superior axis)</td>
</tr>
<tr>
<td>Carotid sinus massage/adenosine</td>
<td>Positive QRS concordance</td>
</tr>
<tr>
<td>terminates arrhythmia</td>
<td>(R wave across chest leads)</td>
</tr>
<tr>
<td></td>
<td>VT</td>
</tr>
<tr>
<td></td>
<td>Negative QRS concordance</td>
</tr>
<tr>
<td></td>
<td>(S wave across chest leads)</td>
</tr>
<tr>
<td></td>
<td>May suggest VT</td>
</tr>
<tr>
<td></td>
<td>Axis shift during arrhythmia</td>
</tr>
<tr>
<td></td>
<td>VT (polymorphic)</td>
</tr>
</tbody>
</table>

*If patient >65 yr and previous MI or structural heart disease, then chance of VT >95%

**May terminate VT in some patients with no structural heart disease

Torsades de Pointes

- a variant of polymorphic VT that occurs in patients with baseline QT prolongation – "twisting of the points"
- looks like usual VT except that QRS complexes "rotate around the baseline" changing their axis and amplitude
- ventricular rate >100 bpm, usually 150-300 bpm
- etiology: predisposition in patients with prolonged QT intervals
  - congenital long QT syndromes
  - drugs: e.g. class IA (quinidine), class III (sotalol), phenothiazines (TCAs), erythromycin, quinolones, antihistamines
  - electrolyte disturbances: hypokalemia, hypomagnesemia
  - nutritional deficiencies causing above electrolyte abnormalities
- treatment: IV magnesium, temporary pacing, isoproterenol and correct underlying cause of prolonged QT, electrical cardioversion if hemodynamic compromise

Arrhythmias that May Present as a Wide QRS Tachycardia

- VT
- SVT with aberrant conduction (rate related)
- SVT with preexisting BBB or nonspecific intraventricular conduction defect
- AV conduction through a bypass tract in WPW patients during an atrial tachyarrhythmia (e.g. atrial flutter, atrial tachycardia)
- Antidromic AVRT in WPW patients (see Pre-Excitation Syndromes, C21)
**Electrophysiology Studies**

- invasive test for the investigation and treatment of cardiac rhythm disorders using intracardiac catheters
- provide detailed analysis of the arrhythmia mechanism and precise site of origin when ECG data are nondiagnostic or unobtainable
- bradycardias: define the mechanisms of SA node dysfunction and localize site of AV conduction block
- tachyarrhythmias: map for possible ablation or to assess inducibility of VT

**Electrical Pacing**

- the decision to implant a pacemaker usually is based on symptoms of a bradyarrhythmia or tachyarrhythmia in the setting of heart disease

**Pacemaker Indications**

- SA node dysfunction (most common): symptomatic bradycardia ± hemodynamic instability
- common manifestations include: syncope, presyncope, or severe fatigue
- SA nodal dysfunction is commonly caused by: intrinsic disease within the SA node (e.g. idiopathic degeneration, fibrosis, ischemia, or surgical trauma), abnormalities in autonomic nervous system function, and drug effects
- AV nodal-infranodal block: Mobitz II, complete heart block

**Pacemaker Complications**

- complications related to surgical implantation include venous access (pneumothorax, hemothorax, air embolism), pacemaker leads (perforation, malposition), pocket hematomas and infection
- complications specific to the pacemaker include a failure to pace, failure to sense, pulse generator failure, pacemaker syndrome and pacemaker mediated tachycardia

**Pacing Techniques**

- temporary: transvenous (jugular, subclavian, femoral) or external (transcutaneous) pacing
- permanent: transvenous into RA, apex of RV, or both
- new generation: rate responsive, able to respond to physiologic demand
- biventricular

**Implantable Cardioverter Defibrillators**

- sudden cardiac death (SCD) usually results from ventricular fibrillation (VFib), sometimes preceded by monomorphic or polymorphic ventricular tachycardia (VT)
- ICDs detect ventricular tachyarrhythmias and are highly effective in terminating VT/VFib and in aborting SCD
- mortality benefit vs. antiarrhythmics in secondary prevention
- benefit seen in patients with ischemic and non-ischemic cardiomyopathy, depressed left ventricular ejection fraction (LVEF), prolonged QRS
- see *Heart Failure*, C36 for current treatment recommendations
Catheter Ablation

Techniques
- Radiofrequency (RF) ablation: a low-voltage high-frequency form of electrical energy (similar to cautery); RF ablation produces small, homogeneous, necrotic lesions approximately 5-7 mm in diameter and 3-5 mm in depth.
- Cryoablation: new technology which uses a probe with a tip that can decrease in temperature to -20°C and -70°C. Produces small, necrotic lesions similar to RF ablation; when brought to -20°C, the catheter tip reversibly freezes the area; bringing the tip down to -70°C for 5 min permanently scars the tissue.
- Advantage: can “test” areas before committing to an ablation.
- Disadvantage: takes much longer than RF (5 min per cryoablation vs. 1 min per RF ablation).

Indications
- Paroxysmal SVT: AVNRT accounts for more than half of all cases.
- Accessory pathway (orthodromic reciprocating tachycardia): 30% of SVT.
- Corrected by targeting the accessory pathway.
- Atrial flutter: reentry pathway in right atrium.
- AFib: potential role for pulmonary vein ablation.
- Ventricular tachycardia: focus arises from the right ventricular outflow tract and less commonly originates in the inferoseptal left ventricle near the apex (note: majority of cases of VT are due to scarring from previous MI and cannot be ablated).

Major Complications
- 1% of patients.
- Death: 0.1-0.2%.
- Cardiac: high grade AV block requiring permanent pacemaker (less risk with cryoablation), tamponade, pericarditis.
- Vascular: hematoma, vascular injury, thromboembolism, TIA/stroke.
- Pulmonary: PE.

Ischemic Heart Disease

Epidemiology
- Most common cause of cardiovascular morbidity and mortality.
- Canadian-led INTERHEART study showed that 9 modifiable risk factors accounted for >90% of MI.
- Atherosclerosis and thrombosis are the most important pathogenetic mechanisms.
- M:F = 2:1 with all age groups included (Framingham study), 8:1 for age <40, 1:1 for age >70.
- According to the Framingham Heart Study, men develop coronary heart disease at a rate double that of women for age <60; incidence in women triples shortly after menopause.
- Peak incidence of symptomatic IHD is age 50-60 (men) and 60-70 (women).
- For primary prevention of ischemic heart disease see Family Medicine, FM7.

Table 7. Risk Factors and Markers for Atherosclerotic Heart Disease

<table>
<thead>
<tr>
<th>Non-Modifiable Risk Factors</th>
<th>Modifiable Risk Factors</th>
<th>Markers of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Hyperlipidemia*</td>
<td>Elevated lipoprotein(a)</td>
</tr>
<tr>
<td>Male, postmenopausal female</td>
<td>HTN*</td>
<td>Hyperhomocysteinemia</td>
</tr>
<tr>
<td>Family history (FHx) of MI*</td>
<td>DM*</td>
<td>Elevated high-sensitivity C-reactive protein (hsCRP)</td>
</tr>
<tr>
<td>First degree male relative &lt;55</td>
<td>Cigarette smoking*</td>
<td>Coronary artery calcification</td>
</tr>
<tr>
<td>First degree female relative &lt;65</td>
<td>Psychosocial stress</td>
<td>Carotid IMT/plaque</td>
</tr>
<tr>
<td></td>
<td>Obesity</td>
<td>Ankle-brachial index</td>
</tr>
<tr>
<td></td>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heavy alcohol intake</td>
<td></td>
</tr>
</tbody>
</table>

* Major risk factor
Chronic Stable Angina

Definition
- Symptom complex resulting from an imbalance between oxygen supply and demand in the myocardium

Etiology and Pathophysiology
- Factors that decrease myocardial oxygen supply
  - Decreased luminal diameter: atherosclerosis, vasospasm
  - Decreased duration of diastole: tachycardia (decreased duration of diastolic coronary perfusion)
  - Decreased hemoglobin: anemia
  - Decreased \( \text{SaO}_2 \): hypoxemia
  - Congenital anomalies
- Factors that increase myocardial oxygen demand
  - Increased heart rate: hyperthyroidism
  - Increased contractility: hyperthyroidism
  - Increased wall stress: myocardial hypertrophy, aortic stenosis

Signs and Symptoms
- Typical: (1) retrosternal chest pain, tightness or discomfort radiating to left (± right) shoulder/arm/neck/jaw, associated with diaphoresis, nausea, anxiety; (2) predictably precipitated by the "3 Es": exertion, emotion, eating; (3) brief duration, lasting <10-15 min and typically relieved by rest and nitrates
- Atypical/probable angina (meets 2 of the above); non-cardiac chest pain (meets <1 of the above)
- Levine’s sign: clutching fist over sternum when describing chest pain
- Anginal equivalents: dyspnea, acute LV failure, flash pulmonary edema

Clinical Assessment
- History including directed risk factor assessment and physical exam
- Labs: Hb, fasting glucose, fasting lipid profile
- ECG (at rest and during episode of chest pain if possible)
- CXR (suspected heart failure, valvular disease, pericardial disease, aortic dissection/aneurysm, or signs or symptoms of pulmonary disease)
- Stress testing (see Stress Testing, C13) or angiography
- Echo
- To assess systolic murmur suggestive of aortic stenosis, mitral regurgitation, and/or HCM
- To assess LV function in patients with Hx of prior MI, pathological Q waves, signs or symptoms of CHF

Differential Diagnosis
- See Differential Diagnosis of Common Presentations, C4
Treatment of Chronic Stable Angina
1. General Measures
   - goals: to reduce myocardial oxygen demand and/or increase oxygen supply
   - lifestyle modification (diet, exercise)
   - treatment of risk factors: statins (see Endocrinology, E2, Family Medicine, FM9 for target lipid guidelines), antihypertensives, etc.
   - pharmacological therapy to stabilize the coronary plaque to prevent rupture and thrombosis
2. Antiplatelet Therapy (first-line therapy)
   - ASA
   - clopidogrel when ASA absolutely contraindicated
3. β-blockers (first-line therapy – improve survival in patients with hypertension)
   - increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
   - cardioselective agents preferred (e.g. metoprolol, atenolol) to avoid peripheral effects (inhibition of vasodilation and bronchodilation via β2 receptors)
   - avoid intrinsic sympathomimetics (e.g. acebutolol) which increase demand
4. Nitrates (symptomatic control, no clear impact on survival)
   - decrease preload (venous dilatation) and afterload (arteriolar dilatation), and increase coronary perfusion
   - maintain daily nitrate-free intervals to prevent tolerance (tachyphylaxis)
5. Calcium Channel Blockers (CCBs, second-line or combination)
   - increase coronary perfusion and decrease demand (HR, contractility) and BP (afterload)
   - caution: verapamil/diltiazem combined with β-blockers may cause symptomatic sinus bradycardia or AV block
6. ACE Inhibitors (ACEI, not used to treat symptomatic angina)
   - angina patients tend to have risk factors for CV disease which warrant use of an ACEI (e.g. HTN, DM, proteinuric renal disease, previous MI with LV dysfunction)
   - benefit in all patients at high risk for CV disease (concomitant DM, renal dysfunction, or LV systolic dysfunction)
   - angiotensin II receptor blockers (ARBs) can be used when ACEI contraindicated; avoid combining ACEI and ARB (e.g. hypersensitivity, angioedema)
7. Invasive Strategies
   - revascularization (see Coronary Revascularization, C33 and COURAGE trial sidebar)

VARIANT ANGINA (Prinzmetal’s Angina)
- myocardial ischemia secondary to coronary artery vasospasm, with or without atherosclerosis
- uncommonly associated with infarction or LV dysfunction
- typically occurs between midnight and 8 am, unrelated to exercise, relieved by nitrates
- typically ST elevation on ECG
- diagnosed by provocative testing with ergot vasoconstrictors (rarely done)
- treat with nitrates and CCBs

SYNDROME X
- typical symptoms of angina but normal angiogram
- may show definite signs of ischemia with exercise testing
- thought to be due to inadequate vasodilator reserve of coronary resistance vessels
- better prognosis than overt epicardial atherosclerosis

Acute Coronary Syndromes

Definition
- ACS includes the spectrum of UA, NSTEMI, and STEMI; this distinction aids in providing the appropriate therapeutic intervention
- MI is defined by evidence of myocardial necrosis. It is diagnosed by a rise/fall of serum markers plus any one of
  - symptoms of ischemia (chest/upper extremity/mandibular/epigastric discomfort; dyspnea)
  - ECG changes (ST-T changes, new BBB or pathological Q waves)
  - imaging evidence (myocardial loss of viability, wall motion abnormality, or intracoronary thrombus)
- if biomarker changes are unattainable, cardiac symptoms combined with new ECG changes is sufficient
- NSTEMI meets criteria for myocardial infarction without ST elevation or BBB
- STEMI meets criteria for myocardial infarction characterized by ST elevation or new BBB
• UA is clinically defined by any of the following:
  ▪ accelerating pattern of pain: increased frequency, increased duration, decreased threshold of exertion, decreased response to treatment
  ▪ angina at rest
  ▪ new-onset angina
  ▪ angina post-MI or post-procedure (e.g. percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG])

Investigations
• history and physical
  ▪ note that up to 30% of MIs are unrecognized or “silent” due to atypical symptoms – more common in women, DM, elderly, post-heart transplant (because of denervation)
• ECG
• CXR
• labs
  ▪ serum cardiac biomarkers for myocardial damage (repeat 8 h later) (see Cardiac Biomarkers, C11)
  ▪ CBC, INR/PTT, electrolytes and magnesium, creatinine, urea, glucose, serum lipids
  ▪ draw serum lipids within 24-48 h because values are unreliable from 2-48 d post-MI

MANAGEMENT OF ACUTE CORONARY SYNDROMES

1. General Measures
• ABCs: assess and correct hemodynamic status first
• bed rest, cardiac monitoring, oxygen
• nitroglycerin SL followed by IV
• morphine IV

2. Anti-Platelet and Anticoagulation Therapy
• see also CCS Antiplatelet Guidelines 2012 for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
• ASA chewed
• NSTEMI
  ▪ ticagrelor in addition to ASA or if ASA contraindicated, subcutaneous low molecular weight heparin or IV unfractionated heparin (UFH) (LMWH preferable, except in renal failure or if CABG is planned within 24 h)
  ▪ clopidogrel used if patient ineligible for ticagrelor
• if PCI is planned: ticagrelor or prasugrel and consider IV GP IIb/IIIa inhibitor (e.g. abciximab)
  ▪ clopidogrel used if patient ineligible for ticagrelor and prasugrel
• prasugrel contraindicated in those with a history of stroke/TIA, and avoidance of or lower dose is recommended for those >75 yr old or weighing under 60 kg (TRITON-TIMI 38)
• anticoagulation options depend on reperfusion strategy:
  ▪ primary PCI: UFH during procedure; bivalirudin is a possible alternative
  ▪ thrombolysis: LMWH (enoxaparin) until discharge from hospital; can use UFH as alternative because of possible rescue PCI
  ▪ no reperfusion: LMWH (enoxaparin) until discharge from hospital
• continue LMWH or UFH followed by oral anticoagulation at discharge if at high risk for thromboembolic event (large anterior MI, AFib, severe LV dysfunction, CHF, previous DVT or PE, or echo evidence of mural thrombus)

3. β-blockers
• STEMI: contraindications include signs of heart failure, low output states, risk of cardiogenic shock, heart block, asthma or airway disease; initiate orally within 24 h of diagnosis when indicated
• if β-blockers are contraindicated or if β-blockers/nitrates fail to relieve ischemia, non-dihydropyridine calcium channel blockers (e.g. diltiazem, verapamil) may be used as second-line therapy in the absence of severe LV dysfunction or pulmonary vascular congestion (calcium channel blockers do not prevent MI or decrease mortality)

4. Invasive Strategies and Reperfusion Options
• UA/NSTEMI: early coronary angiography ± revascularization if possible is recommended with any of the following high-risk indicators:
  ▪ recurrent angina/ischemia at rest despite intensive anti-ischemic therapy
  ▪ CHF or LV dysfunction
  ▪ hemodynamic instability
  ▪ high (≥3) TIMI risk score (tool used to estimate mortality following an ACS)
  ▪ sustained ventricular tachycardia
  ▪ dynamic ECG changes
  ▪ high-risk findings on non-invasive stress testing
PCI within the previous 6 mo
- repeated presentations for ACS despite treatment and without evidence of ongoing ischemia or high risk features
- note: thrombolysis is NOT administered for UA/NSTEMI

- STEMI
  - after diagnosis of STEMI is made, do not wait for results of further investigations before implementing reperfusion therapy
  - goal is to re-perfuse artery: thrombolysis (“EMS-to-needle”) within 30 min or primary PCI (“EMS-to-balloon”) within 90 min (depending on capabilities of hospital and access to hospital with PCI facility)
  - thrombolysis
    - preferred if patient presents ≤12 h of symptom onset, and <30 min after presentation to hospital, has contraindications to PCI, or PCI cannot be administered within 90 min
  - PCI
    - early PCI (≤12 h after symptom onset and <90 min after presentation) improves mortality vs. thrombolysis with fewer intra-cranial hemorrhages and recurrent MIs
    - primary PCI: without prior thrombolytic therapy – method of choice for reperfusion in experienced centres (JAMA 2004;291:736-739)
    - rescue PCI: following failed thrombolytic therapy (diagnosed when following thrombolysis, ST segment elevation fails to resolve below half its initial magnitude and patient still having chest pain)

![Figure 36. Reperfusion strategy in STEMI](image)

**Table 8. Contraindications for Thrombolysis in STEMI**

<table>
<thead>
<tr>
<th>Absolute</th>
<th>Relative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior intracranial hemorrhage</td>
<td>Chronic, severe, poorly controlled HTN</td>
</tr>
<tr>
<td>Known structural cerebral vascular lesion</td>
<td>Uncontrolled HTN (sBP &gt; 180, dBP &gt; 110)</td>
</tr>
<tr>
<td>Known malignant intracranial neoplasm</td>
<td>Current anticoagulation</td>
</tr>
<tr>
<td>Significant closed-head or facial trauma (≤3 mo)</td>
<td>Noncompressible vascular punctures</td>
</tr>
<tr>
<td>Ischemic stroke (≤3 mo)</td>
<td>Ischemic stroke (≥3 mo)</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>Recent internal bleeding (≤2-4 wk)</td>
</tr>
<tr>
<td>Suspected aortic dissection</td>
<td>Prolonged CPR or major surgery (≤3 wk)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Active peptic ulcer disease</td>
</tr>
</tbody>
</table>

**Long-Term Management of ACS**

- risk of progression to MI or recurrence of MI or death is highest within 1 mo
- at 1-3 mo after the acute phase, most patients resume a clinical course similar to that in patients with chronic stable coronary disease
- pre-discharge workup: ECG and echo to assess residual LV systolic function
- drugs required in hospital to control ischemia should be continued after discharge in all patients
- other medications for long-term management of ACS are summarized below

**1. General Measures**

- education
- risk factor modification
2. Antiplatelet and Anticoagulation Therapy
- see also CCS Antiplatelet Guidelines 2012 for details (free mobile apps available on iOS and Android platforms in the CCS app stores)
- ECASA 81 mg daily
- ticagrelor 90 mg twice daily or prasugrel 10 mg daily (at least 1 mo, up to 9-12 mo, if stent placed at least 12 mo)
- clopidogrel 75 mg daily can be used as alternatives to ticagrelor and prasugrel when indicated
- ± warfarin x 3 mo if high risk (large anterior MI, LV thrombus, LVEF <30%, history of VTE, chronic AFib)

3. β-Blockers (e.g. metoprolol 25-50 mg bid or atenolol 50-100 mg daily)

4. Nitrates
- alleviate ischemia but do not improve outcome
- use with caution in right-sided MI patients who have become preload dependent

5. Calcium Channel Blockers (NOT recommended as first line treatment, consider as alternative to β-blockers)

6. Angiotensin-Converting Enzyme Inhibitors
- prevent adverse ventricular remodelling
- recommended for asymptomatic high-risk patients (e.g. diabetics), even if LVEF >40%
- used for symptomatic CHF, reduced LVEF (<40%), anterior MI
- use ARBs in patients who are intolerant of ACEI; avoid combing ACE and ARB

7. ± Aldosterone Antagonists
- if on ACEI and β-blockers and LVEF <40% and CHF or DM
- significant mortality benefit shown with eplerenone by 30 d

8. Statins (early, intensive, irrespective of cholesterol level; e.g. atorvastatin 80 mg daily)

9. Invasive Cardiac Catheterization if indicated (risk stratification)

Figure 37. Post-MI risk stratification

Prognosis following STEMI
- 5-15% of hospitalized patients will die
  - risk factors
    - infarct size/severity
    - age
    - comorbid conditions
    - development of heart failure or hypotension
- post-discharge mortality rates
  - 6-8% within first year, half of these within first 3 mo
  - 4% per year following first yr
- risk factors
  - LV dysfunction
  - residual myocardial ischemia
  - ventricular arrhythmias
  - history of prior MI
Table 9. Complications of Myocardial Infarction

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Presentation</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arrhythmia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Tachycardia</td>
<td>Sinus, AFib, VT, VFib</td>
<td>First 48 h</td>
<td>See Arrhythmias, C17</td>
</tr>
<tr>
<td>2. Bradycardia</td>
<td>Sinus, AV block</td>
<td>First 48 h</td>
<td></td>
</tr>
<tr>
<td>Myocardial Rupture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. LV free wall</td>
<td>Transmural infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>2. Papillary muscle (MR)</td>
<td>Inferior infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>3. Ventricular septum (VSD)</td>
<td>Septal infarction</td>
<td>1-7 d</td>
<td>Surgery</td>
</tr>
<tr>
<td>Shock/CHF</td>
<td>Infarction or aneurysm</td>
<td>Within 48 h</td>
<td>Inotropes, intra-aortic balloon pump</td>
</tr>
<tr>
<td>Post-Infarct Angina</td>
<td>Persistent coronary stenosis</td>
<td>Anytime</td>
<td>Aggressive medical therapy</td>
</tr>
<tr>
<td></td>
<td>Multivessel disease</td>
<td></td>
<td>PCI or CABG</td>
</tr>
<tr>
<td>Recurrent MI</td>
<td>Recoeclussion</td>
<td>Anytime</td>
<td>Aggressive medical therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>PCI or CABG</td>
</tr>
<tr>
<td>Thromboembolism</td>
<td>Mural/apical thrombus</td>
<td>7-10 d, up to 6 mo</td>
<td>Anticoagulation</td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Inflammatory</td>
<td>1-7 d</td>
<td>ASA</td>
</tr>
<tr>
<td>Dressler’s Syndrome</td>
<td>Autoimmune</td>
<td>2-8 wk</td>
<td></td>
</tr>
</tbody>
</table>

Complication Etiology Presentation Therapy

**Treatment Algorithm for Chest Pain**

![Treatment Algorithm for Chest Pain](image)

**Enoxaparin vs. Unfractionated Heparin with Fibrinolysis for ST-elevation Myocardial Infarction**

**AEJM 2008;354:1477-1488**

**Study:** Prospective multicentre RCT.

**Patients:** 20,479 patients (median age 60 yr, 77% male) with STEMI who were scheduled to undergo fibrinolysis.

**Intervention:** Patients were randomized to receive either enoxaparin or weight based unfractionated heparin in addition to thrombolysis and standard therapies.

**Primary Outcome:** Death or recurrent nonfatal MI 30 d post event.

**Results:** The composite primary outcome occurred less often in the enoxaparin group compared with those who received unfractionated heparin (9.9% vs. 12.0%, p=0.001; NNT=43). Taken separately, there was a trend toward reduced mortality (6.9% vs. 7.5%, p=0.11) and a significant reduction in nonfatal reinfarction (5.0% vs. 4.3%, p=0.001) in the enoxaparin group. The risk of major bleeding was significantly increased in the enoxaparin group (2.1% vs. 1.4%, p<0.001, NNI=142).

**Conclusion:** In patients with STEMI receiving thrombolysis, enoxaparin is superior to unfractionated heparin in preventing recurrent nonfatal MI and may lead to a small reduction in mortality.

**Intensive vs. Moderate Lipid Lowering with Statins after Acute Coronary Syndromes**

**AEJM 2004;350:1495-1504**

**Study:** Prospective, double blind, RCT; mean follow-up of 2 yr.

**Population:** 4,162 patients who had been hospitalized for an ACS within the preceding 10 d.

**Intervention:** Patients were randomized to receiving pravastatin 40 mg or atorvastatin 80 mg daily.

**Primary Outcome:** Composite of death from any cause, myocardial infarction, documented unstable angina requiring rehospitalization, revascularization (performed at least 30 d after randomization), and stroke.

**Results:** High dose atorvastatin was associated with a 16% hazard ratio reduction (p=0.005; 99% CI 5-26%) in the primary outcome compared to standard dose pravastatin.

**Conclusions:** In patients who recently experienced an ACS, high dose statin therapy provides greater protection against death and major cardiovascular events than standard dose therapy.

---

**Figure 38. Treatment algorithm for patients with symptoms suggestive of an acute coronary syndrome**

**Sudden Cardiac Arrest**

**Definition**
- unanticipated, non-traumatic cardiac death in a stable patient which occurs within 1 h of symptom onset; VFib is most common cause

**Etiology**
- primary cardiac pathology
  - ischemia/MI
  - LV dysfunction
  - severe ventricular hypertrophy
    - HCM
    - AS
  - congenital heart disease e.g. arrhythmogenic right ventricular dysplasia
  - mutations in cardiac ion channels e.g. long QT syndrome, Brugada syndrome

**Management**
- acute: resuscitate with prompt CPR and defibrillation
- investigate underlying cause (cardiac catheterization, electrophysiologic studies, echo)
- treat underlying cause
- antiarrhythmic drug therapy: amiodarone, β-blockers
- implantable cardioverter defibrillator (ICD)
- refer to ACLS guidelines (see Anesthesia, A33)

**Coronary Revascularization**

**PERCUTANEOUS CORONARY INTERVENTION**
- interventional cardiology technique aimed at relieving significant coronary stenosis
- main techniques: balloon angioplasty, stenting
- less common techniques: rotational/directional/extraction atherectomy

**Indications**
- medically refractory angina
- NSTEMI/UA with high risk features (e.g. high TIMI risk score)
- primary/rescue PCI for STEMI

**Balloon Angioplasty and Intracoronary Stenting**
- coronary lesions dilated with balloon inflation
- major complication is restenosis (approximately 15% at 6 mo), felt to be due to elastic recoil and neointimal hyperplasia
- majority of patients receive intracoronary stent(s) to prevent restenosis
  - bare metal stent (BMS) versus drug-eluting stents: FRAMI trial demonstrated stenting non-culprit lesions results in 14% absolute risk reduction of cardiac death, nonfatal MI, or refractory angina
  - coated with antiproliferative drugs (sirolimus, paclitaxel, everolimus)
  - reduced rate of neointimal hyperplasia and restenosis compared to BMS (5% vs. 20%)
- complication: late stent thrombosis (5 events per 1,000 stents implanted)

**Adjunctive Therapies**
- ASA and heparin decrease post-procedural complications
- further reduction in ischemic complications has been demonstrated using GPIIb/IIIa inhibitors (abciximab, eptifibatide, tirofiban) in coronary angiography and stenting
- following stent implantation
  - dual antiplatelet therapy (ASA and clopidogrel) for 1 mo with BMS or ≥12 mo with DES
  - DAPT study showed benefit of dual antiplatelet therapy beyond 12 mo
  - ASA and prasugrel can be considered for those at increased risk of stent thrombosis

**Procedural Complications**
- mortality and emergency bypass rates <1%
- nonfatal MI: approximately 2-3%

**CORONARY ARTERY BYPASS GRAFT SURGERY**
- objective of CABG is complete reperfusion of the myocardium
Indications
- **CABG**
  - ≥50% diameter stenosis in the left main coronary artery
  - ≥70% diameter stenosis in three major coronary arteries
  - ≥70% diameter stenosis in the proximal LAD artery plus one other major coronary artery
  - survivors of sudden cardiac arrest with presumed ischemia-mediated VT caused by significant (≥70% diameter) stenosis in a major coronary artery
- **other**
  - ≥70% diameter stenosis in two major coronary arteries (without proximal LAD disease) and evidence of extensive ischemia
  - ≥70% diameter stenosis in the proximal LAD artery and evidence of extensive ischemia
  - LV systolic dysfunction (LVEF 35% to 50%) and significant multivessel CAD or proximal LAD stenosis where viable myocardium is present in the region of intended revascularization
- **PCI**
  - UA/NSTEMI if not a CABG candidate
  - STEMI when PCI can be performed more rapidly and safely than CABG
  - CABG or PCI
  - one or more significant (≥70% diameter) coronary artery stenosis amenable to revascularization and unacceptable angina despite medical therapy

**Table 10. Choice of Revascularization Procedure**

<table>
<thead>
<tr>
<th>PCI</th>
<th>CABG</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td><strong>Greater ability to achieve complete revascularization</strong></td>
</tr>
<tr>
<td>Less invasive technique</td>
<td>Decreased need for repeated revascularization procedures</td>
</tr>
<tr>
<td>Decreased periprocedural morbidity and mortality</td>
<td></td>
</tr>
<tr>
<td>Shorter periprocedural hospitalization</td>
<td></td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td><strong>Indications</strong></td>
</tr>
<tr>
<td>Single or double-vessel disease</td>
<td>Triple-vessel or left main disease</td>
</tr>
<tr>
<td>Inability to tolerate surgery</td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Plaque morphology unfavourable for PCI</td>
</tr>
</tbody>
</table>

**Table 11. Conduits for CABG**

<table>
<thead>
<tr>
<th>Graft</th>
<th>Occlusion/Patency Rate</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saphenous Vein Grafts (SVG)</td>
<td>At 10 yr, 50% occluded, 25% stenotic, 25% angiographically normal</td>
<td>Used when arterial grafts are not available or many grafts are required, such as triple or quadruple bypass</td>
</tr>
<tr>
<td>Left Internal Thoracic/Mammary Artery (LITA/LIMA) (LIMA to LAD)</td>
<td>90-95% patency at 15 yr</td>
<td>Most preferred option because of excellent patency, improved event-free survival (angina, MI), decreased late cardiac events, no increase in operative risk</td>
</tr>
<tr>
<td>Right Internal Thoracic/Mammary Artery (RITA/RIMA)</td>
<td>Pedicled RIMA patency comparable to LIMA, Free RIMA patency less</td>
<td>Used in bilateral ITA/IMA grafting, patients receiving bilateral ITAs/IMAs have less risk of recurrent angina, late MI, angioplasty</td>
</tr>
<tr>
<td>Radial Artery (free graft)</td>
<td>85-90% patency at 5 yr</td>
<td>Prone to severe vasospasm post-operatively due to muscular wall</td>
</tr>
<tr>
<td>Right Gastroepiploico Artery</td>
<td>80-90% patency at 5 yr</td>
<td>Primarily used as an in situ graft to bypass the RCA, use limited because of the fragile quality of the artery, other technical issues, increased operative time (laparotomy incision), and incisional discomfort with associated ileus</td>
</tr>
</tbody>
</table>

**Complete Arterial Revascularization**
- For younger patients (<60 yr of age), is preferred due to longer term graft patency

**Redo Bypass Grafting**
- Operative mortality 2.3x higher than first operation 10% perioperative MI rate
- Recommeration undertaken only in symptomatic patients who have failed medical therapy and in whom angiography has documented progression of the disease
- Increased risk with redo-sternotomy secondary to adhesions which may result in laceration to aorta, RV, IMA/ITA, and other bypass grafts

**Percutaneous Coronary Intervention vs. Coronary-Artery Bypass Grafting for Severe Coronary Artery Disease: The SYNTAX Trial**
- **Study**: Prospective RCT.
- **Population**: 1,800 patients with untreated three-vessel or left main coronary artery disease and anatomically equivalent for both Percutaneous Intervention (PCI) and Coronary Artery Bypass Graft (CABG).
- **Intervention**: PCI vs. CABG.
- **Outcome**: Composite of death from any cause, stroke, MI, or repeat revascularization in 12 mo post-intervention.
- **Results**: Incidence of primary outcome was lower in the CABG intervention vs. PCI (12.4% vs. 17.1%, p=0.002, NNT=19). PCI was associated with significantly higher rates of repeat revascularization (13.5% vs. 5.9%, p<0.001) and cardiac death (3.7% vs. 2.1%, p=0.05), while CABG had higher rates of stroke (2.2% vs. 0.6%, p=0.03).
- **Conclusions**: In patients with three-vessel or left main coronary artery disease, CABG is superior to PCI in preventing major adverse cardiovascular and cerebrovascular events within 12 mo of intervention.
Operative Issues

- left ventricular (LV) function is an important determinant of outcome of all heart diseases
- patients with severe LV dysfunction usually have poor prognosis, but surgery can sometimes dramatically improve LV function
- assess viability of non-functioning myocardial segments in patients with significant LV dysfunction using delayed thallium myocardial imaging, stress echocardiography, PET scanning, or MRI

**CABG and Antiplatelet Regimens**

- please refer to CCS guidelines – 2012 update on antiplatelet therapy – for more information if possible
- prior to CABG, clopidogrel and ticagrelor should be discontinued for 5 d and prasugrel for 7 d before surgery
- dual antiplatelet therapy should be continued for 12 mo in patients with ACS within 48-72 h after CABG
- ASA (81 mg) continued indefinitely (can be started 6 h after surgery)
- patients requiring CABG after PCI should continue their dual antiplatelet therapy as recommended in the post-PCI guidelines

### Table 12. Risk Factors for CABG Mortality and Morbidity (decreasing order of significance)

<table>
<thead>
<tr>
<th>Risk Factors for CABG Mortality</th>
<th>Risk Factors for CABG Post-Operative Morbidity or Increased Length of Stay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urgency of surgery (emergent or urgent)</td>
<td>Reoperation</td>
</tr>
<tr>
<td>Reoperation</td>
<td>Emergent procedure</td>
</tr>
<tr>
<td>Older age</td>
<td>Pre-operative intra-aortic balloon pump (IABP)</td>
</tr>
<tr>
<td>Poor left ventricular function (see below)</td>
<td>CHF</td>
</tr>
<tr>
<td>Female gender</td>
<td>CABG + valve surgery</td>
</tr>
<tr>
<td>Left main disease</td>
<td>Older age</td>
</tr>
<tr>
<td>Others include catastrophic conditions (cardiogenic shock, ventricular septal rupture, ongoing CPR), dialysis-dependent renal failure, end-stage COPD, DM, cerebrovascular disease, and peripheral vascular disease</td>
<td>Renal dysfunction</td>
</tr>
<tr>
<td></td>
<td>COPD</td>
</tr>
<tr>
<td></td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular disease</td>
</tr>
</tbody>
</table>

### Procedural Complications

- CABG using cardiopulmonary bypass (CPB)
  - stroke and neurocognitive defects (microembolization of gaseous and particulate matter)
  - immunosuppression
  - systemic inflammatory response leading to
    - myocardial dysfunction
    - renal dysfunction
    - neurological injury
    - respiratory dysfunction
    - coagulopathies

### OFF-PUMP CORONARY ARTERY BYPASS SURGERY

**Procedure**

- avoids the use of CPB by allowing surgeons to operate on a beating heart
  - stabilization devices (e.g. Genzyme Immobilizer) hold heart in place allowing operation while positioning devices (Medtronic Octopus® and Starfish® system) allow the surgeon to lift the beating heart to access the lateral and posterior vessels
  - procedure is safe and well tolerated by most patients; however, this surgery remains technically more demanding

**Indications**

- used in poor candidates for CPB who have: calcified aorta, poor LVEF, severe peripheral vascular disease (PVD), severe COPD, chronic renal failure, coagulopathy, transfusion objections (e.g. Jehovah’s Witness), good target vessels, anterior/lateral wall revascularization, target revascularization in older, sicker patients
- **absolute contraindications**: hemodynamic instability, poor quality target vessels including intramyocardial vessels, diffusely diseased vessels, and calcified coronary vessels
- **relative contraindications**: cardiomegaly/CHF, critical left main disease, small distal targets, recent or current acute MI, cardiogenic shock, LVEF <35%

**Outcomes**

- OPCAB decreases in-hospital morbidity (decreased incidence of chest infection, inotropic requirement, supraventricular arrhythmia), blood product transfusion, ICU stay, length of hospitalization, and CK-MB and troponin I levels
- no significant difference in terms of survival at 2 yr, frequency of cardiac events (MI, PCI, CHF, recurrent angina, redo CABG), or medication usage compared to on-pump CABG
Congestive Heart Failure

Low-Output HF
- Systolic Dysfunction
  - Injury and ischaemia in myocardium
  - Decreased cardiac output
- Diastolic Dysfunction
  - Ineffective ventricular filling

High-Output HF
- Systolic Dysfunction
  - Inflammation and fibrosis
  - Increased cardiac output
- Diastolic Dysfunction
  - Thickened myocardium

Increased Cardiac Workload
- Myocardial stress
- Volume overload
- Pressure overload

Compensation
- Increased heart rate
- Myocardial contractility
- Increased blood volume

Decompensation
- Deterioration of heart function
- Heart unable to maintain blood circulation

Systemic Response
- Activation of SNS and RAAS activity

Table 13. Signs and Symptoms of Left vs. Right Heart Failure

<table>
<thead>
<tr>
<th>Low Cardiac Output (Forward)</th>
<th>Right Cardiac Output (Backward)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
<td>Dyspnea, orthopnea, PND</td>
</tr>
<tr>
<td>Syncope</td>
<td>Cough</td>
</tr>
<tr>
<td>Systemic hypotension</td>
<td>Cracksles</td>
</tr>
<tr>
<td>Cool extremities</td>
<td>Pericardial effusions</td>
</tr>
<tr>
<td>Peripheral cyanosis</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Cool capillary refill</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pulmonary artery</td>
<td>Pericardial effusions</td>
</tr>
<tr>
<td>Mitrail regurgitation</td>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>S3</td>
<td>Pulmonary edema</td>
</tr>
</tbody>
</table>

Does this Dyspneic Patient in the Emergency Department have Congestive Heart Failure?
JAMA 2005;294:1944-1956

LR + (95% CI)
Initial clinical judgment 4.4 (1.8-10.0)
Past Medical History
Heart failure 5.8 (4.1-8.0)
Myocardial infarction 3.1 (2.0-4.9)
Coronary artery disease 1.8 (1.1-2.8)

LR – (95% CI)
Initial clinical judgment 0.45 (0.28-0.73)
Past Medical History
Heart failure 0.45 (0.38-0.53)
Myocardial infarction 0.69 (0.58-0.82)
Coronary artery disease 0.68 (0.48-0.96)

Symptoms
Paroxysmal nocturnal dyspnea 2.6 (1.5-4.5)
Orthopnea 2.2 (1.2-3.9)
Dyspnea on exertion 1.3 (1.2-1.4)

LR – (95% CI)
Initial clinical judgment 0.45 (0.28-0.73)
Past Medical History
Heart failure 0.45 (0.38-0.53)
Myocardial infarction 0.69 (0.58-0.82)
Coronary artery disease 0.68 (0.48-0.96)

Physical Exam
Third heart sound 11 (4.9-25)
Jugular venous distension (3.2-7.9) 0.57-0.77
Rales 2.8 (1.9-4.1)
Pulmonary venous congestion 12 (6.0-21)
Interstitial edema 12 (5.2-27)
Cardiomegaly 3.3 (2.4-4.7)

ECG
Atrial fibrillation 3.8 (1.7-8.8)
Any abnormal finding 2.2 (1.0-4.1)

Dichotomies of Heart Failure
- Forward vs. backward
- Left-sided vs. right-sided
- Systolic vs. diastolic dysfunction
- Low output vs. high output

Use Ejection Fraction to Grade LV Dysfunction
- Grade I (EF > 60%) (Normal)
- Grade II (EF = 40-59%)
- Grade III (EF = 21-39%)
- Grade IV (EF ≤20%)
Pathophysiology
- most common causes are ischemic heart disease, hypertension and valvular heart disease
- myocardial insult causes pump dysfunction/impaired filling leading to myocardial remodelling
  - pressure overload (e.g. AS or HTN) leads to compensatory hypertrophy (concentric remodelling) and eventually interstitial fibrosis
  - volume overload (e.g. AI) leads to dilatation (eccentric remodelling)
- both processes lead to maladaptive changes contributing to disease process
- results in decreased volume cardiac output resulting in activation of the SNS and RAAS
- Na⁺ and water retention, increasing preload and afterload, tachycardia
- perpetuates cycle of increasing cardiac demand and decompensation

Heart Failure with Reduced Ejection Fraction
- impaired myocardial contractile function → decreased LVEF and SV → decreased CO

Volume Overload and Eccentric Remodeling is the Typical Phenotype
- findings: apex beat displaced, S3, cardiothoracic ratio >0.5, decreased LVEF, LV dilatation
- causes
  - ischemic (e.g. extensive CAD, previous MI)
  - non-ischemic
    - HTN
    - DM
    - alcohol (and other toxins)
    - myocarditis
    - dilated cardiomyopathy (multiple causes – see Dilated Cardiomyopathy, C42)

Heart Failure with Preserved Ejection Fraction
- previously known as “diastolic heart failure”
- concentric remodeling with a “stiff” left ventricle is the typical phenotype
- 1/2 of patients with heart failure have preserved EF; confers similar prognosis to HRoEF; more common in the elderly and females
- reduced LV compliance causes increased LV filling pressures, increased LA pressure/volume, and pulmonary congestion
- findings: HTN, apex beat sustained, S4, normal-sized heart on CXR, IVH on ECG/echo, normal EF
- causes
  - transient ischemia (relaxation of myocardium is active and requires ATP)
  - permanent
    - severe hypertrophy (HTN, aortic stenosis, HCM)
    - restrictive cardiomyopathy (e.g. amyloid)
    - MI

High-Output Heart Failure
- caused by demand for increased cardiac output
- often exacerbates existing heart failure or decompensates a patient with other cardiac pathology
- differential diagnosis: anemia, thiamine deficiency (beriberi), hyperthyroidism, A-V fistula or L-R shunting, Paget’s disease, renal disease, hepatic disease

Precipitants of Symptomatic Exacerbations
- consider natural progression of disease vs. new precipitant
- always search for reversible cause
- differential diagnosis can also be organized as follows
  - new cardiac insult/disease: MI, arrhythmia, valvular disease
  - new demand on CV system: HTN, anemia, thyrotoxicosis, infection, etc.
  - medication non-compliance
  - dietary indiscretion e.g. salt intake
  - obstructive sleep apnea

Investigations
- identify and assess precipitating factors and treatable causes of CHF
- blood work: CBC, electrolytes (including calcium and magnesium), BUN, creatinine, fasting blood glucose, HbA1c, lipid profile, liver function tests, serum TSH ± ferritin, BNP, uric acid
- ECG: look for chamber enlargement, arrhythmia, ischemia/infarction
- CXR: cardiomegaly, pleural effusion, redistribution, Kerley B lines, bronchial-alveolar cuffing
- echo: systolic function (LVEF), diastolic function (E/A ratio, E/e’), cardiac dimensions, wall motion abnormalities, RVSP (from TR jet), valvular disease, pericardial effusion
- radionuclide angiography: LVEF
- myocardial perfusion scintigraphy (thallium or sestamibi SPECT)
Acute Treatment of Pulmonary Edema
- treat acute precipitating factors (e.g. ischemia, arrhythmias)
- L – Lasix® (furosemide) 40-500 mg IV
- M – morphine 2-4 mg IV: decreases anxiety and preload (venodilation)
- N – nitroglycerin: topical/IV/SL - use with caution in preload-dependent patients (e.g. right HF or RV infarction) as it may precipitate CV collapse
- O – oxygen: in hypoxemic patients
- P – positive airway pressure (CPAP/BiPAP): decreases preload and need for ventilation when appropriate
- P – position: sit patient up with legs hanging down unless patient is hypotensive
- in ICU setting or failure of LMNOPP, other interventions may be necessary
  - nitroprusside IV
  - hydralazine PO
  - sympathomimetics
    - dopamine
      - low dose: selective renal vasodilation (high potency D1 agonist)
      - medium dose: inotropic support (medium potency β1 agonist)
      - high dose: increases SVR (low potency β1 agonist), which is undesirable
  - dobutamine
    - β1-selective agonist causing isotropy, tachycardia, hypotension (low dose) or hypertension (high dose); most serious side effect is arrhythmia, especially AF
  - phosphodiesterase inhibitors (milrinone)
    - inotropic effect and vascular smooth muscle relaxation (decreased SVR), similar to dobutamine
- consider pulmonary artery catheter to monitor pulmonary capillary wedge pressure (PCWP)
- if patient is unstable or a cardiac etiology is uncertain (PCWP >18 indicates likely cardiac etiology)
- mechanical ventilation as needed
- rarely used, but potentially life-saving measures:
  - intra-aortic balloon pump (IABP) - reduces afterload via systolic unloading and improves coronary perfusion via diastolic augmentation
  - left or right ventricular assist device (LVAD/RVAD)
  - cardiac transplant

Long-Term Management
- overwhelming majority of evidence-based management applies to HREF
- currently no proven pharmacologic therapies shown to reduce mortality in HFPEF; control risk factors (e.g. hypertension)

Conservative Measures
- symptomatic measures: oxygen in hospital, bedrest, elevate the head of bed
- lifestyle measures: diet, exercise, DM control, smoking cessation, decrease alcohol consumption, patient education, sodium and fluid restriction
- multidisciplinary heart failure clinics: for management of individuals at higher risk, or with recent hospitalization

Non-Pharmacological Management
- from CCS guidelines (2013 update)
- cardiac rehabilitation: participation in a structured exercise program for NYHA class I-III after clinical status assessment to improve quality of life (HF-ACTION trial)

Pharmacological Therapy

1. Renin-angiotensin-aldosterone blockade
  - ACEI: standard of care – slows progression of LV dysfunction and improves survival
  - all symptomatic patients functional class II-IV
  - all asymptomatic patients with LVEF <40%
  - post-MI
  - angiotensin II receptor blockers
    - second-line to ACEI if not tolerated, or as adjunct to ACEI if β-blockers not tolerated
    - combination with ACEI is not routinely recommended and should be used with caution as it may precipitate hyperkalemia, renal failure, the need for dialysis and increase (CHARM, ONTARGET)
  - combination angiotensin II receptor blockers with neprilysin inhibitors (ARNI) is a new class of medication that has morbidity and mortality benefit over ACE inhibitor alone; this may become standard first line therapy

2. β-blockers: slow progression and improve survival
  - class I-III with LVEF <40%
  - stable class IV patients
  - carvedilol improves survival in class IV HF (COMET)
  - note: should be used cautiously, titrate slowly because may initially worsen CHF
3. Mineralocorticoid receptor (aldosterone) antagonists: mortality benefit in symptomatic heart failure and severely depressed ejection fraction
   - spironolactone or eplerenone symptomatic heart failure in patients already on ACEI, beta blocker and loop diuretic
   - note: potential for life threatening hyperkalemia
   - monitor K+ after initiation and avoid if Cr >220 µmol/L or K+ >5.2 mmol/L

4. Diuretics: symptom control, management of fluid overload
   - furosemide (40-500 mg daily) for potent diuresis
   - metolazone may be used with furosemide to increase diuresis
   - furosemide, metolazone, and thiazides oppose the hyperkalemia that can be induced by β-blockers, ACEI, ARBs, and aldosterone antagonists

5. Digoxin and cardiac glycosides: digoxin improves symptoms and decreases hospitalizations, no effect on mortality
   - indications: patient in sinus rhythm and symptomatic on ACEI, or CHF and AFib
   - patients on digitalis glycosides may worsen if these are withdrawn

6. Antiarrhythmic drugs: for use in CHF with arrhythmia
   - can use amiodarone, β-blocker, or digoxin

7. Anticoagulants: warfarin for prevention of thromboembolic events
   - prior thromboembolic event or AFib, presence of LV thrombus on echo

Procedural Interventions
- resynchronization therapy: symptomatic improvement with biventricular pacemaker
- consider if QRS >150 msec, LVEF <35%, and persistent symptoms despite optimal therapy
- greatest benefit likely with marked LV enlargement, mitral regurgitation, QRS >150 msec,
- ICD: mortality benefit in 1st prevention of sudden cardiac death
- prior MI, optimal medical therapy, LVEF <30%, clinically stable
- prior MI, non-sustained VT, LVEF 30-40%, EPS inducible VT
- LVAD/RVAD (see Ventricular Assist Devices, C40)
- cardiac transplantation (see Cardiac Transplantation, C40)
- valve repair if patient is surgical candidate and has significant valve disease contributing to CHF (see Valvular Heart Disease, C4)

Sleep-Disordered Breathing
- 45-55% of patients with CHF have sleep disturbances, including Cheyne-Stokes breathing and sleep apnea (central or obstructive)
- associated with a worse prognosis and greater LV dysfunction
- nasal continuous positive airway pressure (CPAP) is effective in treating symptoms of sleep apnea with secondary beneficial effects in cardiac function and symptoms
Cardiac Transplantation

- treatment for end-stage heart disease; due to ischemic or non-ischemic cardiomyopathy
- worldwide 1 yr survival is 85-90%, 5 yr survival about 60%, annual mortality rate of 4%
- matching is according to blood type, body size and weight (should be within 25%), and HLA tissue matching (if time allows)

Indications for Surgery
- severe cardiac disability despite maximal medical therapy (e.g. recurrent hospitalizations for CHF, NYHA III or IV, peak metabolic oxygen consumption <14 mL/kg/min in absence of β-blocker)
- symptomatic cardiac ischemia refractory to conventional treatment (e.g. unstable angina not amenable to CABG or PCI with LVEF <30%; recurrent, symptomatic ventricular arrhythmias)
- exclusion of all surgical alternatives to cardiac transplantation

Prerequisites
- psychosocial stability
- medically compliant and motivated
- relative contraindications: incurable malignancy, major systemic illness, irreversible major organ disease, active systemic infection, obesity, irreversible pulmonary HTN (pulmonary vascular resistance [PVR] >6 Wood units), severe COPD (FEV1 <1 L) or active drug addiction or alcoholism

Complications
- rejection
  - common, <5% have serious hemodynamic compromise
  - gold standard to detect rejection: endomyocardial biopsy
  - risk of acute rejection is greatest during the first 3 mo after transplant
- infection
  - leading cause of morbidity and mortality after cardiac transplantation
  - risk peaks early during the first few months after transplantation and then declines to a low persistent rate
- allograft CAD
  - approximately 50% develop graft CAD within 5 yr of transplantation
  - most common cause of late death following transplantation
- malignancy
  - develops in 15% of cardiac transplant recipients due to immunosuppressive medication
  - second most common cause of late death following transplantation
- cutaneous neoplasms most common, followed by non-Hodgkin's lymphoma and lung cancer
- immunosuppressive medication side effects (prednisone, cyclosporine, tacrolimus, sirolimus)

Ventricular Assist Devices

- work to unload the ventricle while maintaining output; also results in decreased myocardial oxygen consumption permitting recovery of the myocardium that is not irreversibly injured
- can support the left (LVAD), right (RVAD), or both ventricles (BiVAD)
- indications
  - bridge to transplantation, bridge to decision (for transplant), or long term permanent therapy (“destination therapy”)
  - post-operative mechanical support when unable to separate from cardiopulmonary bypass despite inotropic and intra-aortic balloon pump (IABP) support
    - IABP is a catheter based device inserted into the femoral artery and advanced to the descending aorta that decreases myocardial O2 demand and increases blood flow to coronary arteries
  - inflation of the balloon occurs during diastole to increase ascending aorta and coronary artery perfusion pressure; deflation occurs at systole to reduce intra-aortic pressure thus reducing afterload
  - post-operative cardiogenic shock

REMATCH Trial
NEJM 2001;345:1435-1443
Increased survival of 23% vs. 8% with LVAD vs. medical management of heart failure after 2 yr. Heartmate VAD has a biologic surface therefore does not require long-term anticoagulation but appears to improve the clinical course of the heart allograft recipient.

Effects of Donor Pre-Treatment with Dopamine on Survival After Heart Transplantation: A Cohort Study of Heart Transplant Recipients Nested in a Randomized Controlled Multicentre Trial
J Am Coll Cardiol 2010;56:1768-1777
Treatment of brain-dead donors with dopamine of 4 μg/kg/min will not harm cardiac allografts but appears to improve the clinical course of the heart allograft recipient.

Canadian Cardiovascular Society Focused Position Statement Update on Assessment of the Cardiac Patient for Fitness to Drive: Fitness following Left Ventricular Assist Device Implantation
Can J Cardio 2012;28:137-140
Patients with a continuous flow, NYHA class HB, LVAD that are stable 2 mo post LVAD implantation qualify for private driving only and are disqualified from commercial driving.
**Myocardial Disease**

**Definition of Cardiomyopathy**
- intrinsic or primary myocardial disease not secondary to congenital, hypertensive, coronary, valvular, or pericardial disease
- functional classification: dilated, hypertrophic, or restrictive
- LV dysfunction 2º to MI often termed “ischemic cardiomyopathy”, is not a true cardiomyopathy (i.e. primary myocardial disorder) since the primary pathology is obstructive CAD

<table>
<thead>
<tr>
<th>Dilated Cardiomyopathy</th>
<th>Secondary Causes</th>
<th>Hypertrophic Cardiomyopathy</th>
<th>Restrictive Cardiomyopathy</th>
<th>Secondary Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic, infectious (e.g. myocarditis), alcohol, familial, collagen vascular disease, etc.</td>
<td>CAD, MI, DM, valvar (e.g. AR, MR)</td>
<td>Genetic disorder affecting cardiac sarcomeres (most common cause of sudden cardiac death in young athletes)</td>
<td>Amyloidosis, sarcoidosis, scleroderma, hemochromatosis, Fabry’s, Pompe’s Disease, Loeffler’s, etc.</td>
<td>HTN, DM, valvar (e.g. AS), post-MI, transiently by ischemia, etc.</td>
</tr>
</tbody>
</table>

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**Myocarditis**

**Definition**
- inflammatory process involving the myocardium ranging from acute to chronic; an important cause of dilated cardiomyopathy

**Etiology**
- idiopathic
- infectious
  - viral: *S. aureus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia*
  - bacterial: *S. aureus, C. perfringens, C. diphtheriae, Mycoplasma, Rickettsia*
  - fungi
  - spirochetal (*Lyme disease – Borrelia burgdorferi*)
  - Chagas disease (*Trypanosoma cruzi*)
- toxic: catecholamines, chemotheraphy, cocaine
- hypersensitivity/eosinophilic: drugs (antibiotics, diuretics, lithium, clozapine), insect/snake bites
- systemic diseases: collagen vascular diseases (SLE, rheumatoid arthritis, others), sarcoidosis, autoimmune
- other: giant cell myocarditis, acute rheumatic fever

**Signs and Symptoms**
- constitutional symptoms
- acute CHF - dyspnea, tachycardia, elevated JVP
- chest pain – due to pericarditis or cardiac ischemia
- arrhythmias
- systemic or pulmonary emboli
- pre-syncope/syncope/sudden death

**Investigations**
- ECG: non-specific ST-T changes ± conduction defects
- blood work
  - increased CK, troponin, LDH, and AST with acute myocardial necrosis ± increased WBC, ESR, ANA, rheumatoid factor, complement levels
  - blood culture, viral titres and cold agglutinins for Mycoplasma
- CXR: enlarged cardiac silhouette
- echo: dilated, hypokinetic chambers, segmental wall motion abnormalities
- cardiovascular magnetic resonance: functional and morphological abnormalities as well as tissue pathology (gadolinium enhancement)
- myocardial biopsy

**Management**
- supportive care
- restrict physical activity
- treat CHF
- treat arrhythmias
- anticoagulation
- treat underlying cause if possible
Prognosis
• often unrecognized, and may be self-limited
• myocarditis treatment trial showed 5yr mortality between 25-50%
• giant cell myocarditis, although rare can present with fulminant CHF and be rapidly fatal, with 5yr mortality >80%
• sudden death in young adults
• may progress to dilated cardiomyopathy

Dilated Cardiomyopathy

Definition
• unexplained dilation and impaired systolic function of one or both ventricles

Etiology
• idiopathic (presumed viral or idiopathic) ~50% of DCM
• alcohol
• familial/genetic
• uncontrolled tachycardia (e.g. persistent rapid AFib)
• collagen vascular disease: SLE, polyarteritis nodosa, dermatomyositis, progressive systemic sclerosis
• infectious: viral (coxsackie B, HIV), Chagas disease, Lyme disease, Rickettsial diseases, acute rheumatic fever, toxoplasmosis
• neuromuscular disease: Duchenne muscular dystrophy, myotonic dystrophy, Friedreich's ataxia
• metabolic: uremia, nutritional deficiency (thiamine, selenium, carnitine)
• endocrine: hyper/hypothyroidism, DM, pheochromocytoma
• peripartum
• toxic: cocaine, heroin, organic solvents
• drugs: chemotherapies (doxorubicin, cyclophosphamide), anti-retrovirals, chloroquine, clozapine, TCA
• radiation

Signs and Symptoms
• may present as
  • CHF
  • systemic or pulmonary emboli
  • arrhythmias
  • sudden death (major cause of mortality due to fatal arrhythmia)

Investigations
• blood work: CBC, electrolytes, Cr, bicarbonate, BNP, CK, troponin, LFTs, TSH, TIBC
• ECG: variable ST-T wave abnormalities, poor R wave progression, conduction defects (e.g. BBB), arrhythmias (non-sustained VT)
• CXR: global cardiomegaly (globular heart), signs of CHF, pleural effusion
• echocardiography: chamber enlargement, global hypokinesis, depressed LVEF, MR and TR, mural thrombi
• endomyocardial biopsy: not routine, used to rule out a treatable cause
• coronary angiography: in selected patients to exclude ischemic heart disease

Management
• treat underlying disease: e.g. abstinence from alcohol
• treat CHF: see Heart Failure, C36
• thromboembolism prophylaxis: anticoagulation with warfarin
• indicated for: AFib, history of thromboembolism or documented thrombus
• treat symptomatic or serious arrhythmias
• immunize against influenza and S. pneumoniae
• consider surgical options (e.g. LVAD, transplant, volume reduction surgery) in appropriate candidates with severe, drug refractory disease
• consider ICD among patients with a LVEF <30%

Prognosis
• depends on etiology
• better with reversible underlying cause, worst with infiltrative diseases, HIV, drug-induced
• cause of death usually CHF (due to pump failure) or sudden death 2° to ventricular arrhythmias
• systemic emboli are significant source of morbidity
• 20% mortality in 1st yr, 10% per year after
Hypertrophic Cardiomyopathy

Definition
- Defined as unexplained ventricular hypertrophy
- Various patterns of HCM are classified, but most causes involve pattern of septal hypertrophy

Etiology and Pathophysiology
- Histopathologic features include myocyte disarray, myocyte hypertrophy, and interstitial fibrosis
- Cause is felt to be a genetic defect involving one of the cardiac sarcomeric proteins (>400 mutations associated with autosomal dominant inheritance, incomplete penetrance)
- Prevalence of 1/500-1/1,000 in general population
- Generally presents in early adulthood

Hemodynamic Classification
- Hypertrophic obstructive cardiomyopathy (HOCM): dynamic LV outflow tract (LVOT) obstruction, either at rest or with provocation, defined as LVOT gradient of at least 30 mmHg
  - Dynamic i.e. obstruction (and the murmur) is reduced with maneuvers that increase preload, and augmented with maneuvers that reduce preload
- Non-obstructive HCM: no LVOT obstruction
- Many patients have diastolic dysfunction (impaired ventricular filling secondary to LV hypertrophy which decreases compliance)

Signs and Symptoms
- Clinical manifestations: asymptomatic (common, therefore screening is important), SOB on exertion, angina, presyncope/syncope (due to LV outflow obstruction or arrhythmia), CHF, arrhythmias, SCD
- Pulses: rapid upstroke, "spike and dome" pattern in carotid pulse (in HCM with outflow tract obstruction)
- Precordial palpation: PMI localized, sustained, double impulse, ‘triple ripple’ (triple apical impulse in HOCM), LV lift
- Precordial auscultation: normal or paradoxically split S2, S4, harsh systolic diamond-shaped murmur at LLSB or apex, enhanced by squat to standing or Valsalva (murmur secondary to LVOT obstruction as compared to AS); often with pansystolic murmur due to mitral regurgitation

Investigations
- ECG/Holter monitor: LVH, high voltages across precordium, prominent Q waves (lead I, aVL, V5, V6), tall R wave in V1, P wave abnormalities
- Transthoracic echocardiography and echo-Doppler study: asymmetric septal hypertrophy (less commonly apical), systolic anterior motion (SAM) of mitral valve and MR; LVOT gradient can be estimated by Doppler measurement
- Genetic studies (± magnetic resonance imaging) can be helpful when echocardiography is inconclusive for diagnosis
- Cardiac catheterization (only when patient being considered for invasive therapy)

Management
- Avoid factors which increase obstruction (e.g. volume depletion)
  - Avoidance of all competitive sports
- Treatment of obstructive HCM
  - Medical agents: β-blockers, disopyramide, verapamil (started only in monitored setting), phenylephrine (in setting of cardiogenic shock)
  - Avoid nitrates, diuretics, and ACEI as they increase LVOT gradient and worsen symptoms
- Patients with obstructive HCM and drug-refractory symptoms
  - Surgical myectomy
  - Alcohol septal ablation - percutaneous Intervention that ablates the hypertrophic septum with 100% ethanol via the septal artery
  - Dual chamber pacing (rarely done)
- Treatment of patients at high risk of sudden death: ICD
- First-degree relatives (children, siblings, parents) of patients with HCM should be screened (physical, ECG, 2D echo) every 12-18 mo during during adolescence, then serially every 5 yr during adulthood
Prognosis
• potential complications: AFib, VT, CHF, sudden cardiac death (1% risk/yr; most common cause of SCD in young athletes)
  ▪ major risk factors for sudden death (consider ICD placement)
  ▪ history of survived cardiac arrest/sustained VT
  ▪ family history of multiple premature sudden deaths
  ▪ other factors associated with increased risk of sudden cardiac death
    • syncope (presumed to be arrhythmic in origin)
    • non-sustained VT on ambulatory monitoring
    • marked ventricular hypertrophy (maximum wall thickness ≥30 mm)
    • abnormal BP in response to exercise (in patients <40 yr old with HCM)

Restrictive Cardiomyopathy

Definition
• impaired ventricular filling with preserved systolic function in a non-dilated, non-hypertrophied ventricle secondary to factors that decrease myocardial compliance (fibrosis and/or infiltration)

Etiology
• infiltrative: amyloidosis, sarcoidosis
• non-infiltrative: scleroderma, idiopathic myocardial fibrosis
• storage diseases: hemochromatosis, Fabry’s disease, Gaucher’s disease, glycogen storage diseases
• endomyocardial
  ▪ endomyocardial fibrosis, Loeffer’s endocarditis, or eosinophilic endomyocardial disease
  ▪ radiation heart disease
  ▪ carcinoid syndrome (may have associated tricuspid valve or pulmonary valve dysfunction)

Clinical Manifestations
• CHF (usually with preserved LV systolic function), arrhythmias
• elevated JVP with prominent x and y descents, Kussmaul’s sign
• S3, S4, MR, TR
• thromboembolic events

Investigations
• ECG: low voltage, non-specific, diffuse ST-T wave changes ± non-ischemic Q waves
• CXR: mild cardiac enlargement
• Echo: LAE, RAE; specific Doppler findings with no significant respiratory variation
• cardiac catheterization: increased end-diastolic ventricular pressures
• endomyocardial biopsy: to determine etiology (especially for infiltrative RCM)

Management
• exclude constrictive pericarditis
• treat underlying disease: control HR, anticoagulate if AFib
• supportive care and treatment for CHF, arrhythmias
• heart transplant: might be considered for CHF refractory to medical therapy

Prognosis
• depends on etiology

Key Investigations
• Echo: may show respiratory variation in blood flow in CP
• CT: may show very thickened pericardium and calcification in CP
• MRI: best modality to directly visualize pericardium and myocardium

RCM vs. Constrictive Pericarditis (CP)
Present similarly but CP is treatable with surgery
Valvular Heart Disease

- see Guidelines on the Management of Valvular Heart Disease. JACC Jun 10;63(22):2438-88 for details

Infective Endocarditis

- see Infectious Diseases, ID16
- American Heart Association (AHA) 2007 guidelines recommend IE prophylaxis
  - only for patients with
    - prosthetic valve material
    - past history of IE
    - certain types of congenital heart disease
    - cardiac transplant recipients who develop valvulopathy
  - only for the following procedures
    - dental
    - respiratory tract
    - procedures on infected skin/skin structures/MSK structures
    - not GI/GU procedures specifically

Rheumatic Fever

- see Pediatrics, P59

Prognosis

- acute complications: myocarditis (DCM/CHF), conduction abnormalities (sinus tachycardia, AFib), valvulitis (acute MR), acute pericarditis (not constrictive pericarditis)
- chronic complications: rheumatic valvular heart disease – fibrous thickening, adhesion, calcification of valve leaflets resulting in stenosis/regurgitation, increased risk of IE ± thromboembolism
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever
- mitral valve most commonly affected

Valve Repair and Valve Replacement

- indication for valve repair or replacement depends on the severity of the pathology; typically recommended when medical management has failed to adequately improve the symptoms or reduce the risk of morbidity and mortality
- pathologies that may require surgical intervention include congenital defects, infections, rheumatic heart disease, as well as a variety of valve diseases associated with aging
- valve repair: balloon valvuloplasty, surgical valvuloplasty (commissurotomy, annuloplasty), chordae tendineae shortening, tissue patch
- valve replacement: typically for aortic or mitral valves only; repair is favored in younger individuals; percutaneous techniques being established

Choice of Valve Prosthesis

<table>
<thead>
<tr>
<th>Table 15. Mechanical Valve vs. Bioprosthetic Valve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical Valve</td>
</tr>
<tr>
<td>Good durability</td>
</tr>
<tr>
<td>Less preferred in small aortic root sizes</td>
</tr>
<tr>
<td>Increased risk of thromboembolism (1-3%/yr): requires long-term anticoagulation with coumadin</td>
</tr>
<tr>
<td>Target INR</td>
</tr>
<tr>
<td>Aortic valves: 2.0-3.0 (mean 2.5)</td>
</tr>
<tr>
<td>Mitral valves: 2.5-3.5 (mean 3.0)</td>
</tr>
<tr>
<td>Increased risk of hemorrhage: 1-2%/yr</td>
</tr>
</tbody>
</table>

Mitrval Valve Repair vs. Replacement for Severe Ischemic Mitral Regurgitation

NEJM 2014;370:23-32

Purpose: Ischemic mitral regurgitation is associated with significant mortality risk. The purpose of this study was to compare the effectiveness and safety of repairing versus replacing the mitral valve in patients with severe chronic ischemic mitral regurgitation.

Study Design: RCT with 251 patients with severe ischemic mitral regurgitation were randomly assigned to mitral valve repair or chordal-sparing replacement. The primary endpoint was the left ventricular end-systolic volume index (LVESVI) at 12 mo.

Results: There were no significant between-group differences in LVESVI, in the rate of major adverse cardiac or cerebrovascular events, in functional status, or in quality of life at 12 mo. The rate of moderate or severe mitral regurgitation recurrence at 12 mo was significantly higher in the repair group than in the replacement group (32.6% vs. 2.3%, respectively).

Conclusions: No significant difference in left ventricular reverse modeling or survival at 12 mo between patients who underwent mitral valve repair or replacement. Replacement provided more durable correction of mitral regurgitation, but there were no significant differences in clinical outcomes.
Table 16. Valvular Heart Disease

<table>
<thead>
<tr>
<th>Problem</th>
<th>Etiology</th>
<th>Definition</th>
<th>Pathophysiology</th>
<th>Symptoms</th>
<th>Physical Exam</th>
<th>Surgical Options</th>
<th>Interventions Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic Stenosis (AS)</td>
<td>Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease</td>
<td>Normal aortic valve area = 3.4 cm²</td>
<td>Volume overload → LV dilatation → increased SV, high sBP and low dBP → increased wall tension → pressure overload → LVH (low dBP → decreased coronary perfusion)</td>
<td>Usually only becomes symptomatic late in disease when LV failure develops</td>
<td>Waterhammer pulse, bispersian pulse, femoral-brachial sBP &gt; 20</td>
<td>Valve replacement: most patients</td>
<td>Percutaneous valve replacement (transfemoral or transapical approach) is an option in selected patients who are not considered good candidates for surgery</td>
</tr>
<tr>
<td>Mitral Stenosis (MS)</td>
<td>Rheumatic disease most common cause, congenital (rare)</td>
<td>Severe MS is mitral valve area (MVA) &lt; 1.2 cm²</td>
<td>Increased LA pressure → pulmonary vascular resistance and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)</td>
<td>DSB on exertion, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)</td>
<td>Physical Exam: Displaced hyperdynamic apex, left parasternal tap, apical thrill</td>
<td>Valve replacement: most patients</td>
<td>Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology (can be determined by echo), asymptomatic pts with moderate-severe MS, pulmonary HTN</td>
</tr>
<tr>
<td>Mitral Regurgitation (MR)</td>
<td>Mitral valve prolapse, congenital cleft leaflets, LV dilation/anuremum (CHF, DCM, myocardin), IE abscess, Marfan’s syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease</td>
<td>Reduced CO → increased LV and LA pressure → LV and LA dilatation → CHF and pulmonary HTN</td>
<td>Redo operation, failure of repair, heavily calcified annulus</td>
<td></td>
<td>Physical Exam: Displaced hyperdynamic apex, left parasternal tap, apical thrill</td>
<td>Valve replacement: most patients</td>
<td>Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology (can be determined by echo), asymptomatic pts with moderate-severe MS, pulmonary HTN</td>
</tr>
<tr>
<td>Aortic Regurgitation (AR)</td>
<td>Supravalvular: aortic root disease (Marfan’s, atherosclerosis and dissecting aneurysm, connective tissue disease) Valvular: congenital (bicuspid aortic valve, large VSD), IE</td>
<td>Acute presentation: IE, aortic dissection, trauma, failed prosthetic valve</td>
<td>Pathophysiology: early decrescendo diastolic murmur at LLB (cusp pathology) or RLSB (aortic root pathology), best heard sitting, leaning forward, on full expiration, soft S1, absent S2, S3 (late)</td>
<td>Usually only becomes symptomatic late in disease when LV failure develops</td>
<td>Physical Exam: Waterhammer pulse, bispersian pulse, femoral-brachial sBP &gt; 20</td>
<td>Valve replacement: most patients</td>
<td>Percutaneous valve replacement (transfemoral or transapical approach) is an option in selected patients who are not considered good candidates for surgery</td>
</tr>
</tbody>
</table>

**Summary of Valvular Disease**

### Aortic Stenosis (AS)
- **Etiology:** Congenital (bicuspid, unicuspid valve), calcification (wear and tear), rheumatic disease
- **Definition:** Normal aortic valve area = 3.4 cm²
  - Mild AS: 1.5 to 3 cm²
  - Moderate AS: 1.0 to 1.5 cm²
  - Severe AS: < 1.0 cm²
- **Pathophysiology:** Outflow obstruction → increased EDP → concentric LVH → LV failure → CHF, subendocardial ischemia
- **Symptoms:** Exertional angina, syncope, dyspnea, PND, orthopnea, peripheral edema
- **Physical Exam:** Narrow pulse pressure, brachial-radial delay, pulsus parvus et tardus, sustained PMI
  - Echocardiography: decreased aortic valve area, pressure gradient, LVH, reduced LV function
- **Investigations:**
  - Electrocardiogram (ECG): LVH and strain, LBBB, LAE, AFib
  - Chest X-ray (CXR): LAE, CHF, aortic valve calcification
  - Echocardiogram (Echo): reduced valve area, pressure gradient, LVH, reduced LV function
- **Treatment:**
  - Asymptomatic: serial echos, avoid exertion
  - Symptomatic: avoid nitrates/arterial dilators and ACEI in severe AS
- **Interventional Options:**
  - Percutaneous balloon valvuloplasty (in very young)
  - Valve replacement
  - Valve repair
- **Surgical Options:**
  - Aortic root replacement (Bentall procedure): when ascending aortic aneurysm present, valve conduit used

### Mitral Stenosis (MS)
- **Etiology:** Rheumatic disease most common cause, congenital (rare)
- **Definition:** Severe MS is mitral valve area (MVA) < 1.2 cm²
- **Pathophysiology:**
  - MS → fixed CO and LAE → increased LA pressure → pulmonary vascular resistance and CHF; worse with AFib (no atrial kick), tachycardia (decreased atrial emptying time) and pregnancy (increased preload)
- **Symptoms:**
  - DSB on exertion, orthopnea, fatigue, palpitations, peripheral edema, malar flush, pinched and blue facies (severe MS)
  - Physical Exam: AFib, no “a” wave on JVP, left parasternal lift, palpable diastolic thrill at apex
  - Auscultation: mid-diastolic rumble at apex, best heard with bell in left lateral decubitus position following exertion, loud S1, OS following loud P2 (heard best during expiration), long diastolic murmur and short A2-OS interval correlate with worse MS
- **Investigations:**
  - ECG: NSR, AFib, LVEF (P mitral), RVH, RAD
  - CXR: LAE, CHF, mitral valve calcification
  - Echo/TTE: shows restricted opening of mitral valve
  - Cath: indicated in concurrent CAD if > 40 yr (male) or > 50 yr (female)
- **Treatment:**
  - Avoid exertion, fever (increased LA pressure), treat AFib and CHF, increase diastolic filling time (I-blockers, digitalis)
  - Surgery if: NYHA class III-IV CHF, LV dilatation/aneurysm (CHF, DCM, myocardin), IE abscess, Marfan’s syndrome, HOCM, acute MI, myxoma, mitral valve annulus calcification, chordae/papillary muscle trauma/ischemia/rupture (acute), rheumatic disease
- **Interventional Options:**
  - Percutaneous balloon valvuloplasty: young rheumatic pts and good leaflet morphology (can be determined by echo), asymptomatic pts with moderate-severe MS, pulmonary HTN
  - Contraindication: left atrial thrombus, moderate MR
- **Surgical Options:**
  - Open Mitral Commissurotomy: if mild calcification + leaflet/chordal thickening
  - Valve replacement: failure of repair, heavily calcified annulus
  - Advantage of repair: low rate of endocarditis, no anticoagulation, less chance of re-operation
Table 16. Valvular Heart Disease (continued)

**Tricuspid Stenosis (TS)**

**Etiology**
Rheumatic disease, congenital, carcinoid syndrome, fibroelastosis; usually accompanied by MS

**Pathophysiology**
Increased RA pressure → right heart failure → decreased CO and fixed on exertion

**Symptoms**
Peripheral edema, fatigue, palpitations

**Physical Exam**
Prominent "a" waves in JVP; +ve abdominojugular reflex, Kussmaul’s sign, diastolic rumble 4th left intercostal space

**Investigations**
ECG: RAE
CXR: dilatation of RA without pulmonary artery enlargement
Echo: diagnostic

**Treatment**
Preload reduction (diuretics), slow HR, surgery if: only if other surgery required (e.g. mitral valve replacement)

**Surgical Options**
Valve Replacement:
- Only if severely diseased valve
- Bioprosthesis preferred

**Tricuspid Regurgitation (TR)**

**Etiology**
RV dilation, IE (particularly due to IV drug use), rheumatic disease, congenital (Ebstein anomaly), carcinoid

**Pathophysiology**
RV dilatation → TR → further RV dilatation → right heart failure

**Symptoms**
Peripheral edema, fatigue, palpitations

**Physical Exam**
"cv" waves in JVP; +ve abdominojugular reflex, Kussmaul’s sign, holosystolic murmur at LLSB accentuated by inspiration, left parasternal lift

**Investigations**
ECG: RAE, RV, AFib
CXR: RAE, RV enlargement
Echo: diagnostic

**Treatment**
Preload reduction (diuretics)
Surgery if: only if other surgery required (e.g. mitral valve replacement)

**Surgical Options**
Annuloplasty (i.e. repair, rarely replacement)

**Pulmonary Stenosis (PS)**

**Etiology**
Usually congenital, rheumatic disease (rare), carcinoid syndrome

**Pathophysiology**
Increased RV pressure → RV hypertrophy → right heart failure

**Symptoms**
Chest pain, syncope, fatigue, peripheral edema

**Physical Exam**
Systolic murmur at 2nd left intercostal space accentuated by inspiration, pulmonary ejection click, right-sided S4

**Investigations**
ECG: RVH
CXR: prominent pulmonary arteries enlarged RV
Echo: diagnostically

**Treatment**
Balloon valvuloplasty if severe symptoms

**Surgical Options**
Percutaneous or open balloon valvuloplasty

**Pulmonary Regurgitation (PR)**

**Etiology**
Pulmonary HTN, IE, rheumatic disease, tetralogy of Fallot (post-repair)

**Pathophysiology**
Increased RV volume → increased wall tension → RV hypertrophy → right heart failure

**Symptoms**
Chest pain, syncope, fatigue, peripheral edema

**Physical Exam**
Early diastolic murmur at LLSB, Graham Steell (diastolic) murmur 2nd and 3rd left interspace increasing with inspiration

**Investigations**
ECG: RVH
CXR: prominent pulmonary arteries if pulmonary HTN; enlarged RV
Echo: diagnostic

**Treatment**
Rarely requires treatment; valve replacement (rarely done)

**Surgical Options**
Pulmonary valve replacement

**Mitral Valve Prolapse (MVP)**

**Etiology**
Myxomatous degeneration of chordae, thick, bulky leaflets that crowd orifice, associated with Marfan’s syndrome, pectus excavatum, straight back syndrome, other MSK abnormalities; <3% of population

**Pathophysiology**
Mitral valve displaced into LA during systole; no causal mechanisms found for symptoms

**Symptoms**
Prolonged, stabbing chest pain, dyspnea, anxiety/panic, palpitations, fatigue, presyncope

**Physical Exam**
Auscultation: mid-systolic click (due to billowing of mitral leaflet into LA; tensing of redundant valve tissue); mid to late systolic murmur at apex, accentuated by Valsalva or squat-to-stand maneuvers

**Investigations**
ECG: non-specific ST-T wave changes, paroxysmal SVT, ventricular ectopy
Echo: systolic displacement of thickened mitral valve leaflets into LA

**Treatment**
Asymptomatic: no treatment; reassurance
Symptomatic: ß-blockers and avoidance of stimulants (caffeine) for significant palpitations, anticoagulation if AFib

**Surgical Options**
Mitral valve surgery (repair favoured over replacement) if symptomatic and significant MR
Figure 41. Hemodynamics of aortic stenosis
Stenosis across the aortic valve results in the generation of a significant pressure gradient between the left ventricle and the aorta and a crescendo-decrescendo murmur during systolic contraction. The stenosis decreases the intensity of aortic valve closure hence diminishing S2.

Figure 42. Hemodynamics of aortic regurgitation
Regurgitation across the aortic valve during diastole causes the aortic pressure to rapidly decrease and a decrescendo murmur can be heard at the onset of diastole (after S2 is audible). The presence of regurgitant blood from the aorta increases left-ventricular end-diastolic volume.

Figure 43. Hemodynamics of acute mitral regurgitation
During systolic contraction, blood regurgitates from the left ventricle into the left atrium across the incompetent mitral valve resulting in an audible holosystolic murmur between S1 and S2. The portion of left ventricular end-diastolic volume that regurgitates into the left atrial myocardium increases left atrial pressures resulting in a tall V-wave (in the JVP).

Figure 44. Hemodynamics of mitral stenosis
First note that the left atrial pressure exceeds the left ventricular pressure during diastole due to mitral stenosis and the consequent generation of a pressure gradient across the left atrium and left ventricle. In diastole the stenotic mitral valve opens which corresponds to the opening snap (OS) and the passage of blood across the mitral stenosis results in an audible decrescendo murmur. Left atrial contraction prior to S1 increases the pressure gradient resulting in accentuation of the murmur before S1 is audible.
Pericardial Disease

Acute Pericarditis

Etiology of Pericarditis/Pericardial Effusion
- idiopathic is most common: presumed to be viral
- infectious
  - viral: Coxsackie virus A, B (most common), echovirus
  - bacterial: *S. pneumoniae, S. aureus*
- TB
- fungal: histoplasmosis, blastomycosis
- post-MI: acute (direct extension of myocardial inflammation, 1-7 d post-MI), Dressler’s syndrome (autoimmune reaction, 2-8 wk post-MI)
- post-cardiac surgery (e.g. CABG), other trauma
- metabolic: uremia (common), hypothyroidism
- neoplasm: Hodgkin’s, breast, lung, renal cell carcinoma, melanoma
- collagen vascular disease: SLE, polyarteritis, rheumatoid arthritis, scleroderma
- vascular: dissecting aneurysm
- other: drugs (e.g. hydralazine), radiation, infiltrative disease (sarcoid)

Signs and Symptoms
- diagnostic triad: chest pain, friction rub and ECG changes (diffuse ST elevation and PR depression with reciprocal changes in aVR)
- pleuritic chest pain: alleviated by sitting up and leaning forward
- pericardial friction rub: may be uni-, bi-, or triphasic; evanescent and rare
- ± fever, malaise

Investigations
- ECG: initially diffuse elevated ST segments ± depressed PR segment, the elevation in the ST segment is concave upwards → 2-5 d later ST isoelectric with T wave flattening and inversion
- CXR: normal heart size, pulmonary infiltrates
- Echo: performed to assess for pericardial effusion

Treatment
- treat the underlying disease
- anti-inflammatory agents (high dose NSAIDs/ASA, steroids use controversial), analgesics

Complications
- recurrent episodes of pericarditis, atrial arrhythmia, pericardial effusion, tamponade, constrictive pericarditis

Pericardial Effusion

Etiology
- transudative (serous)
- CHF, hypoalbuminemia/hypoproteinemia, hypothyroidism
- exudative (serosanguinous or bloody)
  - causes similar to the causes of acute pericarditis
  - may develop acute effusion secondary to hemopericardium (trauma, post-MI myocardial rupture, aortic dissection)
- physiologic consequences depend on type and volume of effusion, rate of effusion development, and underlying cardiac disease

Signs and Symptoms
- may be asymptomatic or similar to acute pericarditis
- dyspnea, cough
- extra-cardiac (esophageal/recurrent laryngeal nerve/tracheo-bronchial/phrenic nerve irritation)
- JVP increased with dominant “x” descent
- arterial pulse normal to decreased volume, decreased pulse pressure
- auscultation: distant heart sounds ± rub
- Ewart’s sign

Ewart’s Sign
Bronchial breathing and dullness to percussion at the lower angle of the left scapula in pericardial effusion due to effusion compressing left lower lobe of lung
Investigations
- ECG: low voltage (sum of QRS in I + II + III < 155 or V1 + V2 + V3 < 3010 MM), flat T waves, electrical alternans (classic, but not sensitive to exclude effusion)
- be cautious in diagnosing STEMI in a patient with pericarditis and an effusion - antiplatelets may precipitate hemorrhagic effusion
- CXR: cardiomegaly, rounded cardiac contour
- ER: bedside ultrasound with subxiphoid view showing fluid in pericardial sac
- Echo (procedure of choice): fluid in pericardial sac
- pericardiocentesis: definitive method of determining transudate vs. exudate, identify infectious agents, neoplastic involvement

Treatment
- mild: frequent observation with serial echos, treat underlying cause, anti-inflammatory agents
- severe: treat as in tamponade (see Cardiac Tamponade)

Cardiac Tamponade

Etiology
- major complication of rapidly accumulating pericardial effusion
- cardiac tamponade is a clinical diagnosis
- any cause of pericarditis but especially trauma, malignancy, uremia, proximal aortic dissection with rupture

Pathophysiology
- high intra-pericardial pressure → decreased venous return → decreased diastolic ventricular filling → decreased CO → hypotension and venous congestion

Signs and Symptoms
- tachypnea, dyspnea, shock, muffled heart sounds
- pulsus paradoxus (inspiratory fall in systolic BP > 10 mmHg during quiet breathing)
- JVP “x” descent only, blunted “y” descent
- hepatic congestion/peripheral edema

Investigations
- ECG: electrical alternans (pathognomonic variation in R wave amplitude), low voltage
- echo: pericardial effusion, compression of cardiac chambers (RA and RV) in diastole
- cardiac catheterization

Treatment
- pericardiocentesis: Echo-guided
- pericardiotomy
- avoid diuretics and vasodilators (these decrease venous return to already under-filled RV → decrease LV preload → decrease CO)
- IV fluid may increase CO
- treat underlying cause

Constrictive Pericarditis

Etiology
- chronic pericarditis resulting in fibrosed, thickened, adherent, and/or calcified pericardium
- any cause of acute pericarditis may result in chronic pericarditis
- major causes are idiopathic, post-infectious (viral, TB), radiation, post-cardiac surgery, uremia, MI, collagen vascular disease

Signs and Symptoms
- dyspnea, fatigue, palpitations
- abdominal pain
- may mimic CHF (especially right-sided HF)
  - ascites, hepatosplenomegaly, edema
  - increased JVP, Kussmaul's sign (paradoxical increase in JVP with inspiration), Friedreich's sign (prominent “y” descent)
  - BP usually normal (and usually no pulsus paradoxus)
  - precordial examination: ± pericardial knock (early diastolic sound)
- see Table 17 for differentiation from cardiac tamponade

Investigations
- ECG: non-specific – low voltage, flat T wave, ± AFib
- CXR: pericardial calcification, effusions
- echo/CT/MRI: pericardial thickening
- cardiac catheterization: equalization of end-diastolic chamber pressures (diagnostic)

Treatment
- medical: diuretics, salt restriction
- surgical: pericardiectomy (only if refractory to medical therapy)
- prognosis best with idiopathic or infectious cause and worst in post-radiation; death may result from heart failure
### Table 17. Differentiation of Constrictive Pericarditis vs. Cardiac Tamponade

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Constrictive Pericarditis</th>
<th>Cardiac Tamponade</th>
</tr>
</thead>
<tbody>
<tr>
<td>JVP</td>
<td>“y” &gt; “x”</td>
<td>“x” &gt; “y”</td>
</tr>
<tr>
<td>Kussmaul’s sign</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Pulmonary paradoxicus</td>
<td>Uncommon</td>
<td>Always</td>
</tr>
<tr>
<td>Pericardial knock</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Hypotension</td>
<td>Variable</td>
<td>Severe</td>
</tr>
</tbody>
</table>

### Common Medications

#### ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)
- **Examples**
  - enalapril (Vasotec®)
  - perindopril (Coversyl®)
  - ramipril (Altace®)
  - lisinopril (Zestril®)
- **Mechanism of Action**
  Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis
- **Indications**
  - HTN, CAD, CHF, post-MI, DM
- **Side Effects**
  - Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema
- **Contraindications**
  - Bilateral renal artery stenosis, pregnancy, caution in decreased GFR

#### ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)
- **Examples**
  - candesartan
  - irebesartan
  - valsartan
- **Mechanism of Action**
  Block AT II receptors, causing similar effects to ACEI
- **Indications**
  - Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated
- **Side Effects**
  - Similar to ACEI, but do not cause dry cough
- **Contraindications**
  - Same as ACEI

#### DIRECT RENIN INHIBITORS (DRIs)
- **Examples**
  - aliskiren
- **Mechanism of Action**
  Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I; this also causes a decrease in AT II
- **Indications**
  - HTN (exact role of this drug remains unclear)
- **Side Effects**
  - Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure
- **Contraindications**
  - Pregnancy, severe renal impairment

#### &-BLOCKERS
- **Examples**
  - &1 antagonists
    - atenolol, metoprolol, bisoprolol
  - &1/2 antagonists
    - propranolol
  - &1 antagonists with intrinsic sympathomimetic activity
    - acebutalol
- **Mechanism of Action**
  Block &-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node
- **Indications**
  - HTN, CAD, acute MI, post-MI, CHF (start low and go slow), AFib, SVT
- **Side Effects**
  - Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, Raynaud’s phenomenon, claudication
- **Contraindications**
  - Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW

#### CALCIUM CHANNEL BLOCKERS (CCBs)
- **Examples**
  - Benzothiazepines
    - diltiazem
  - Phenylalkylamines (non-dihydropyridines)
    - verapamil
  - Dihydropyridines
    - amlodipine
    - nifedipine (Adalat®)
    - felodipine (Plendil®)
- **Mechanism of Action**
  Block smooth muscle and myocardial calcium channels causing effects similar to &-blockers
- **Indications**
  - HTN, CAD, SVT, diastolic dysfunction
- **Side Effects**
  - Hypotension, edema, flushing, headache, light-headedness
- **Contraindications**
  - Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW

#### DIURETICS
- **Examples**
  - Thiazides
    - hydrochlorothiazide, chlorothalidone, metolazone
  - Loop diuretics
    - furosemide (Lasix®)
  - Aldosterone receptor antagonists
    - spironolactone
    - eplerenone
- **Mechanism of Action**
  Reduce Na+ reabsorption in the distal convoluted tubule (DCT)
  Blocks Na+ /K+ -ATPase in the loop of Henle
  Antagonize aldosterone receptors
- **Indications**
  - HTN, CHF, hypokalemia
  - Edema, hyperkalemia, gynecomastia
- **Side Effects**
  - Hypotension, polyuria
  - Hypovolemia, hypokalemic metabolic alkalosis
  - Edema, hyperkalemia, anorexia, N/V
- **Contraindications**
  - Sufa allergy, pregnancy
  - Hypovolemia, hypokalemia
  - Renal insufficiency, hyperkalemia, pregnancy

#### INOTROPES
- **Examples**
  - digoxin (Lanoxin®)
- **Mechanism of Action**
  Inhibit Na+ /K+ -ATPase, leading to increased intracellular Na+ and Ca2+ concentration and increased myocardial contractility
  Also slows conduction through the AV node
- **Indications**
  - CHF, AFib
  - AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V
- **Contraindications**
  - 2nd or 3rd degree AV block, hypokalemia, WPW

### Table 18. Commonly Used Cardiac Therapeutics

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACEI)</td>
<td>enalapril (Vasotec®), perindopril (Coversyl®), ramipril (Altace®), lisinopril (Zestril®)</td>
<td>Inhibit ACE-mediated conversion of angiotensin I to angiotensin II (AT II), causing peripheral vasodilation and decreased aldosterone synthesis</td>
<td>HTN, CAD, CHF, post-MI, DM</td>
<td>Dry cough, 10% hypotension, fatigue, hyperkalemia, renal insufficiency, angioedema</td>
<td>Bilateral renal artery stenosis, pregnancy, caution in decreased GFR</td>
</tr>
<tr>
<td>ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs)</td>
<td>candesartan, irebesartan, valsartan</td>
<td>Block AT II receptors, causing similar effects to ACEI</td>
<td>Same as ACEI, although evidence is generally less for ARBs; often used when ACEI are not tolerated</td>
<td>Similar to ACEI, but do not cause dry cough</td>
<td>Same as ACEI</td>
</tr>
<tr>
<td>DIRECT RENIN INHIBITORS (DRIs)</td>
<td>aliskiren</td>
<td>Directly blocks renin thus inhibiting the conversion of angiotensinogen to angiotensin I; this also causes a decrease in AT II</td>
<td>HTN (exact role of this drug remains unclear)</td>
<td>Diarrhea, hyperkalemia (higher risk if used with an ACEI), rash, cough, angioedema, reflux, hypotension, rhabdomyolysis, seizure</td>
<td>Pregnancy, severe renal impairment</td>
</tr>
<tr>
<td>&amp;-BLOCKERS</td>
<td>&amp;1 antagonists</td>
<td>atenolol, metoprolol, bisoprolol</td>
<td>Block &amp;-adrenergic receptors, decreasing HR, BP, contractility, and myocardial oxygen demand, slow conduction through the AV node</td>
<td>Hypotension, fatigue, light-headedness, depression, bradycardia, hyperkalemia, bronchospasm, impotence, depression of counterregulatory response to hypoglycemia, exacerbation of Raynaud’s phenomenon, and claudication</td>
<td>Sinus bradycardia, 2nd or 3rd degree heart block, hypotension, WPW</td>
</tr>
<tr>
<td></td>
<td>&amp;1/2 antagonists</td>
<td>propranolol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&amp;1 antagonists with intrinsic sympathomimetic activity</td>
<td>acebutalol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CALCIUM CHANNEL BLOCKERS (CCBs)</td>
<td>Benzothiazepines</td>
<td>diltiazem</td>
<td>Block smooth muscle and myocardial calcium channels causing effects similar to &amp;-blockers</td>
<td>HTN, CAD, SVT, diastolic dysfunction</td>
<td>Hypotension, bradycardia, edema, Negative inotrope</td>
</tr>
<tr>
<td></td>
<td>Phenylalkylamines (non-dihydropyridines)</td>
<td>verapamil</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dihydropyridines</td>
<td>amlodipine</td>
<td>Block smooth muscle calcium channels causing peripheral vasodilation</td>
<td>HTN, CAD</td>
<td>Hypotension, edema, flushing, headache, light-headedness</td>
</tr>
<tr>
<td></td>
<td></td>
<td>nifedipine (Adalat®), felodipine (Plendil®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIURETICS</td>
<td>Thiazides</td>
<td>hydrochlorothiazide, chlorothalidone, metolazone</td>
<td>Reduce Na+ reabsorption in the distal convoluted tubule (DCT)</td>
<td>HTN (drugs of choice for uncomplicated HTN)</td>
<td>Hypotension, hypokalemia, polyuria, Sufa allergy, pregnancy</td>
</tr>
<tr>
<td></td>
<td>Loop diuretics</td>
<td>furosemide (Lasix®)</td>
<td>Blocks Na+ /K+ -ATPase in the loop of Henle</td>
<td>CHF, pulmonary or peripheral edema</td>
<td>Hypovolemia, hypokalemic metabolic alkalosis, Hypovolemia, hypokalemia</td>
</tr>
<tr>
<td></td>
<td>Aldosterone receptor antagonists</td>
<td>spironolactone, eplerenone</td>
<td>Antagonize aldosterone receptors</td>
<td>HTN, CHF, hypokalemia</td>
<td>Edema, hyperkalemia, gynecomastia, Renal insufficiency, hyperkalemia, pregnancy</td>
</tr>
<tr>
<td>INOTROPES</td>
<td></td>
<td>digoxin (Lanoxin®)</td>
<td>Inhibit Na+ /K+ -ATPase, leading to increased intracellular Na+ and Ca2+ concentration and increased myocardial contractility</td>
<td>CHF, AFib</td>
<td>AV block, tachyarrhythmias, bradyarrhythmias, blurred or yellow vision (van Gogh syndrome), anorexia, N/V</td>
</tr>
</tbody>
</table>


### Table 18. Commonly Used Cardiac Therapeutics (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Examples</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTICOAGULANTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coumarins</td>
<td>warfarin (Coumadin®)</td>
<td>Antagonizes vitamin K, leading to decreased synthesis of clotting factors II, VII, IX, and X</td>
<td>AFib, LV dysfunction, prosthetic valves</td>
<td>Bleeding (by far the most important side effect), paradoxical thrombosis, skin necrosis</td>
<td>Recent surgery or bleeding, bleeding diathesis, pregnancy</td>
</tr>
<tr>
<td>Heparins</td>
<td>Unfractionated heparin LMWHs: dalteparin, enoxaparin, tinzaparin</td>
<td>Antithrombin III agonist, leading to decreased clotting factor activity</td>
<td>Acute MI; when immediate anticoagulant effect needed</td>
<td>Bleeding, osteoporosis, heparin-induced thrombocytopenia (less in LMWHs)</td>
<td>Recent surgery or bleeding, bleeding diathesis, thrombocytopenia, renal insufficiency (for LMWHs)</td>
</tr>
<tr>
<td>Direct thrombin inhibitors</td>
<td>dabigatran, melagatran</td>
<td>Competitive, direct thrombin inhibitor; thrombin enables fibrinogen conversion to fibrin during the coagulation cascade, thereby preventing thrombus development</td>
<td>AFib</td>
<td>Bleeding, GI upset</td>
<td>Severe renal impairment, recent surgery, active bleeding</td>
</tr>
<tr>
<td>Direct Factor Xa inhibitors</td>
<td>rivaroxaban, apixaban, edoxaban</td>
<td>Direct, selective and reversible inhibition of factor Xa in both the intrinsic and extrinsic coagulation pathways</td>
<td>AFib</td>
<td>Bleeding, GI upset, elevated liver enzymes</td>
<td>Hepatic disease, active bleeding, bleeding diathesis, pregnancy, lactation</td>
</tr>
<tr>
<td><strong>ANTIPLATELETS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salicylates</td>
<td>ASA (Aspirin®)</td>
<td>Irreversibly acetylates platelet COX-1, preventing thromboxane A2-mediated platelet aggregation</td>
<td>CAD, acute MI, post-MI, post-PCI, CABG</td>
<td>Bleeding, GI upset, GI ulceration, impaired renal perfusion</td>
<td>Active bleeding or PUD</td>
</tr>
<tr>
<td>Thienopyridines</td>
<td>clopidogrel (Plavix®), ticlopidine (Ticlid®), prasugrel (Effient®)</td>
<td>P2Y12 antagonist (block platelet ADP receptors)</td>
<td>Acute MI, post-MI, post-PCI, CABG</td>
<td>Bleeding, thrombotic thrombocytopenic purpura, neutropenia (ticlopidine)</td>
<td>Active bleeding or PUD</td>
</tr>
<tr>
<td>Nucleoside analogues</td>
<td>ticagrelor (Brilinta®)</td>
<td>P2Y12 antagonist (but different binding site than thienopyridines)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GPIIb/IIIa inhibitors</td>
<td>eptifibatide, tirofiban, abciximab</td>
<td>Block binding of fibrinogen to Gp IIb/IIIa</td>
<td>Acute MI, particularly if PCI is planned</td>
<td>Bleeding</td>
<td>Recent surgery or bleeding, bleeding diathesis</td>
</tr>
<tr>
<td><strong>THROMBOLYICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>alteplase, reteplase, tenecteplase, streptokinase</td>
<td>Convert circulating plasminogen to plasmin, which lyses cross-linked fibrin</td>
<td>Acute STEMI</td>
<td>Bleeding</td>
<td>See Table 8, C30</td>
<td></td>
</tr>
<tr>
<td><strong>NITRATES</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitroglycerin</td>
<td></td>
<td>Relax vascular smooth muscle, producing venous and arteriolar dilation</td>
<td>CAD, MI, CHF (isosorbide dinitrate plus hydralazine)</td>
<td>Headache, dizziness, weakness, postural hypotension</td>
<td>Concurrent use of cGMP phosphodiesterase inhibitors, angle closure glaucoma, increased intracranial pressure</td>
</tr>
<tr>
<td><strong>LIPID LOWERING AGENTS</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Statins</td>
<td>atorvastatin (Lipitor®), pravastatin (Pravachol®), rosuvastatin (Crestor®), simvastatin (Zocor®), lovastatin (Meracor®)</td>
<td>Inhibit HMG-CoA reductase, which catalyzes the rate-limiting step in cholesterol synthesis</td>
<td>Dyslipidemia (1st prevention of CAD), CAD, post-MI (2nd prevention of CV events)</td>
<td>Myalgia, rhabdomyolysis, abdominal pain</td>
<td>Liver or muscle disease</td>
</tr>
<tr>
<td>Cholesterol absorption inhibitor</td>
<td>ezetimibe (Zetrot®)</td>
<td>inhibits gut absorption of cholesterol</td>
<td>Decreases LDL but does not reduce overall mortality</td>
<td>Myalgia, rhabdomyolysis, abdominal pain</td>
<td>Liver or renal impairment</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>fibrates, bile acid sequestrates, nicotinic acid</td>
<td>Primarily in familial hypercholesterolemia</td>
<td></td>
<td>GI side effects common</td>
<td></td>
</tr>
<tr>
<td>Investigational</td>
<td>PSCK9 inhibitor</td>
<td>monoclonal antibody</td>
<td>hypercholesterolemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Antiarrhythmics

Figure 45. Representative cardiac action potential

Table 19. Antiarrhythmic* Drugs (Vaughan-Williams Classification)

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>Indications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>quinidine</td>
<td>SVT, VT</td>
<td>Torsades de Pointes (all Ia), diarrhea</td>
<td>Moderate Na⁺ channel blockade Slows phase 0 upstroke</td>
</tr>
<tr>
<td></td>
<td>procainamide</td>
<td></td>
<td>Lupus-like syndrome</td>
<td>Prolongs repolarization, slowing conduction</td>
</tr>
<tr>
<td></td>
<td>disopyramide</td>
<td></td>
<td>Anticholinergic effects</td>
<td></td>
</tr>
<tr>
<td>Ib</td>
<td>lidocaine</td>
<td>VT</td>
<td>Confusion, stupor, seizures</td>
<td>Mild Na⁺ channel blockade Shortens phase 3 repolarization</td>
</tr>
<tr>
<td></td>
<td>mexiletine</td>
<td></td>
<td>GI upset, tremor</td>
<td></td>
</tr>
<tr>
<td>Ic</td>
<td>propafenone</td>
<td>SVT, VT, AFib</td>
<td>Exacerbation of VT (all Ic)</td>
<td>Marked Na⁺ channel blockade Markedly slows phase 0 upstroke</td>
</tr>
<tr>
<td></td>
<td>flecainide</td>
<td></td>
<td>Negative inotropy (all Ic)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>encainide</td>
<td></td>
<td>Bradycardia and heart block (all Ic)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>propranolol, metoprolol, etc.</td>
<td>SVT, AFb</td>
<td>Bronchospasms, negative inotropy, bradycardia, AV block, impotence, fatigue</td>
<td>β-blocker Decreases phase 4 depolarization</td>
</tr>
<tr>
<td>III</td>
<td>amiodarone**</td>
<td>SVT, VT, AFib</td>
<td>Amiodarone: Photosensitivity, pulmonary toxicity, hepatotoxicity, thyroid disease, increased INR Amiodarone and Sotalol: Torsades de Pointes, bradycardia, heart block, β-blocker side effects</td>
<td>Blocks K⁺ channel Prolongs phase 3 repolarization, which prolongs refractory period</td>
</tr>
<tr>
<td></td>
<td>sotalol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>verapamil, diltiazem</td>
<td>SVT, AFib</td>
<td>Bradycardia, AV block Hypotension</td>
<td>Calcium channel blocker Slows phase 4 spontaneous depolarization, slowing AV node conduction</td>
</tr>
</tbody>
</table>

*All antiarrhythmics have potential to be proarrhythmic **Amiodarone has class I, II, III, and IV properties

Table 20. Actions of α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Target System</th>
<th>α RECEPTORS</th>
<th>β RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α1</td>
<td>α2</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Constriction of vascular smooth muscle</td>
<td>Same as α1</td>
</tr>
<tr>
<td></td>
<td>Constriction of skin, skeletal muscle, and splanchnic vessels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Increased myocardial contractility Decreased heart rate</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Bronchodilation</td>
<td></td>
</tr>
<tr>
<td>Dermal</td>
<td>Pilomotor smooth muscle contraction Apocrine constriction</td>
<td></td>
</tr>
<tr>
<td>Ocular</td>
<td>Radial muscle contraction</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Inhibition of myenteric plexus Anal sphincter contraction</td>
<td></td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Pregnant uterine contraction Penile and seminal vesicle ejaculation Urinary bladder contraction</td>
<td>Smooth muscle wall relaxation Stimulation of renal renin release Bladder wall relaxation</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Stimulate liver gluconeogenesis and glycogenolysis at the liver</td>
<td>Same as α1 Fat cell lipolysis</td>
</tr>
</tbody>
</table>

Adapted from the Family Practice Notebook (www.fpnotebook.com/NEU194.htm)
Table 21. Commonly Used Drugs that Act on α and β Adrenergic Receptors

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>α RECEPTORS</th>
<th>β RECEPTORS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>α1</td>
<td>α1 and α2</td>
</tr>
<tr>
<td>Agonist</td>
<td>Phenylephrine</td>
<td>Epinephrine</td>
</tr>
<tr>
<td></td>
<td>Methoxamine</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>Antagonist</td>
<td>Prazosin</td>
<td>Phentolamine</td>
</tr>
<tr>
<td></td>
<td>Phenoxycbenzamine</td>
<td>Phenylephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Adapted from the Family Practice Notebook (http://www.fpnotebook.com/NEU194.htm)

Landmark Cardiac Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISCHEMIC HEART DISEASE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Lancet 2003; 361:1149-58</td>
<td>In hypertensive patients with risk factors for CHD and average or below-average cholesterol, atorvastatin reduced nonfatal MI, fatal CHD, fatal/nonfatal stroke, coronary events but not all-cause mortality</td>
</tr>
<tr>
<td>CAPRIE</td>
<td>Lancet 1996; 348:1328-39</td>
<td>In atherosclerotic vascular disease clopidogrel reduced the primary combined endpoint of stroke, MI, or vascular death and improved PAD compared to ASA</td>
</tr>
<tr>
<td>CARE</td>
<td>NEJM 1996; 335:1001-9</td>
<td>Pravastatin reduced MI and stroke in patients with previous MI and average cholesterol</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007; 356:1503-16</td>
<td>Compared with optimal medical therapy alone PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>CURE</td>
<td>NEJM 2001; 345:494-502</td>
<td>Clopidogrel plus ASA reduced death from CV causes, non fatal MI, or stroke but increased bleeding complications</td>
</tr>
<tr>
<td>EUROPA</td>
<td>Lancet 2003; 362:782-88</td>
<td>With stable CAD and no CHF perindopril reduced cardiovascular death, MI, and total mortality</td>
</tr>
<tr>
<td>HOPE</td>
<td>NEJM 2000; 342:154-60</td>
<td>In high-risk patients without low LVEF or CHF ramipril reduced rates of death, MI, stroke, revascularization, new diagnosis of DM and complications due to DM; vitamin E had no effect on outcomes</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002; 360:1-12</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths, and major vascular events</td>
</tr>
<tr>
<td>INTERHEART</td>
<td>Lancet 2004; 364:937-52</td>
<td>Nine modifiable risk factors account for 90% of myocardial infarction</td>
</tr>
<tr>
<td>JUPITER</td>
<td>NEJM 2008; 359:2196-2207</td>
<td>With low to normal LDL-C and elevated hsCRP treatment with rosuvastatin significantly reduced major cardiovascular events; NNT with rosuvastatin for 2 yr to prevent one primary endpoint = 95</td>
</tr>
<tr>
<td>SYNTAX</td>
<td>NEJM 2009; 360:961-972</td>
<td>CABG has lower rate of major cardiac or cerebrovascular events; the rate of stroke was increased with CABG, whereas the rate of repeat revascularization was increased with PCI</td>
</tr>
<tr>
<td>TNT</td>
<td>NEJM 2005; 352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d</td>
</tr>
<tr>
<td>WHI</td>
<td>JAMA 2002; 288:321-333</td>
<td>Estrogen plus progestin therapy is associated with increased risks of cardiovascular disease and breast cancer but decreased risks of hip fracture and colorectal cancer in postmenopausal women</td>
</tr>
</tbody>
</table>

MYOCARDIAL INFARCTION

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>BHAJ</td>
<td>JAMA 1982; 247:1707-14</td>
<td>In acute MI propranolol reduced all-cause mortality, cardiovascular death, and sudden death from atherosclerotic heart disease</td>
</tr>
<tr>
<td>COURAGE</td>
<td>NEJM 2007; 356:1503-16</td>
<td>Compared with optimal medical therapy alone PCI + medical therapy did not reduce all-cause mortality and non fatal MI, and it did not reduce the incidence of major cardiovascular events</td>
</tr>
<tr>
<td>DAPT</td>
<td>NEJM 2014; 371:2155-66</td>
<td>Dual antiplatelet therapy beyond one year confers additional benefit</td>
</tr>
</tbody>
</table>
### MYOCARDIAL INFARCTION

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISIS-2</td>
<td>Lancet 1988; 2:349-60</td>
<td>Early therapy with streptokinase and ASA in patients with MI individually and in combination significantly reduced all-cause mortality and in combination demonstrated additive effect</td>
</tr>
<tr>
<td>ISIS-4</td>
<td>Lancet 1995; 345:869-85</td>
<td>In patients with suspected or definite acute MI early treatment with captopril reduced all-cause mortality at 35 d and during long-term follow up</td>
</tr>
<tr>
<td>OASIS-5</td>
<td>NEJM 2006; 354:1464-76</td>
<td>Compared to enoxaparin, fondaparinux reduced mortality rates, major bleeds at 9 and MI at 30 and 180 d</td>
</tr>
<tr>
<td>PEGASUS-TIMI54</td>
<td>NEJM 2015</td>
<td>Ticagrelor on top of ASA reduces CV events and in patients with a history of MI</td>
</tr>
<tr>
<td>PLATO</td>
<td>NEJM 2009; 361:1045-57</td>
<td>ACS patients with either STEMI or NSTEMI, regardless of reperfusion strategy, ticagrelor reduced mortality, MI and stroke without increased bleeding compared to clopidogrel</td>
</tr>
<tr>
<td>PROVE IT – TIMI 22</td>
<td>NEJM 2004; 350:1495-1504</td>
<td>In patients hospitalized for ACS high-dose atorvastatin reduced all-cause mortality, MI, unstable angina, revascularization, and stroke compared with pravastatin</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>NEJM 2007; 357:2001-15</td>
<td>In ACS patients scheduled for PCI, prasugrel reduced ischemic events but increased major bleeding compared to clopidogrel; no change in mortality</td>
</tr>
</tbody>
</table>

### HEART FAILURE

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIRE</td>
<td>Lancet 1993; 342:821-8</td>
<td>Ramipril commenced 3-10 d after MI and continued for a mean 15-month period significantly reduced all-cause mortality in patients with non-severe CHF</td>
</tr>
<tr>
<td>CHARM</td>
<td>Lancet 2003; 362:759-66</td>
<td>Candesartan reduced overall mortality, cardiovascular death, and CHF hospitalizations</td>
</tr>
<tr>
<td>CIBIS II</td>
<td>Lancet 1999; 353:9-13</td>
<td>Bisoprolol reduced all-cause mortality, cardiovascular death, all-cause hospitalization, and CHF hospitalization</td>
</tr>
<tr>
<td>COMET</td>
<td>Lancet 2003; 362:7-13</td>
<td>Carvedilol was associated with a reduction in all cause mortality compared with metoprolol</td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>NEJM 1987; 316:1429-35</td>
<td>Enalapril reduced all-cause mortality, death due to progression of heart failure</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>NEJM 2001; 344:1651-8</td>
<td>Carvedilol in addition to standard treatment significantly reduced the risk of death or hospitalization in patients with severe CHF</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>NEJM 2008; 359:2495-2504</td>
<td>In patients with CHF and normal LVEF treatment with ARB (irbesartan) did not improve mortality or cardiovascular morbidity compared to placebo</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>Lancet 1999; 353:2001-7</td>
<td>Metoprolol CR/XL daily in addition to optimum standard therapy improved survival in clinically stable patients equating to prevention of 1 death per 27 patients treated per year</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>NEJM 2014; 371:993-1004</td>
<td>Novel drug (LCZ696 containing valsartan and a neprilysin inhibitor) (prevents degradation of natriuretic peptides) reduces hospitalization and mortality</td>
</tr>
<tr>
<td>RALES</td>
<td>NEJM 1999; 341:709-17</td>
<td>In severe CHF (class III/IV) and LVEF &lt;35% spironolactone reduced all-cause mortality, sudden death, and death due to progression of heart failure</td>
</tr>
<tr>
<td>SAVE</td>
<td>NEJM 1992; 327:869-77</td>
<td>Patients with LV dysfunction post-MI long-term captopril over 3.5 yr reduced the risk of death due to cardiovascular causes, recurrent MI, development of severe CHF, and CHF hospitalization</td>
</tr>
<tr>
<td>SCD-HeFT</td>
<td>NEJM 2005; 352:225-237</td>
<td>In mild-to-moderate CHF shock-only ICD significantly reduces risk of death; amiodarone had no benefit compared with placebo in treating patients with mild-to-moderate CHF</td>
</tr>
<tr>
<td>SOLVD</td>
<td>NEJM 1991; 325:293-302</td>
<td>In stable chronic CHF with decreased LVEF (&lt;0.35) long-term enalapril reduced death due to all causes and death or hospitalization due to CHF</td>
</tr>
<tr>
<td>TRACE</td>
<td>NEJM 1995; 333:1670-6</td>
<td>In patients with LV dysfunction post-MI long-term trandolapril reduced the risk of death or progression to severe CHF and reduced risk of sudden death</td>
</tr>
<tr>
<td>V-HeFT II</td>
<td>NEJM 1991; 325:303-10</td>
<td>In chronic CHF enalapril reduced mortality more than hydralazine-isosorbide for at least 2 yr; treatment with either enalapril or hydralazine-isosorbide increased LVEF</td>
</tr>
</tbody>
</table>

### DIABETES

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDS</td>
<td>Lancet 2004; 364:685-96</td>
<td>Atorvastatin reduces the risk of cardiovascular events in patients with type 2 DM</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>NEJM 2008; 358:1547-59</td>
<td>In patients with vascular disease or DM without CHF telmisartan is equally as effective as ramipril, with telmisartan causing a reduced risk of cough and angioedema, and an increased risk of hypotensive symptoms; combination therapy offers no advantage</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>---------------</td>
<td>------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>ARRHYTMIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFFIRM</td>
<td>NEJM 2002; 347:1825-33</td>
<td>No significant difference in mortality rates between rate or rhythm control of AFib</td>
</tr>
<tr>
<td>AF-CHF</td>
<td>NEJM 2008; 358:2667-77</td>
<td>In patients with AFib and CHF there is no significant difference in mortality rates from cardiovascular causes between rate and rhythm control</td>
</tr>
<tr>
<td>ARISTOTLE</td>
<td>NEJM 2011; 365:981-92</td>
<td>AF patients treated with apixaban had a lower incidence of stroke, major bleeding and mortality compared to warfarin</td>
</tr>
<tr>
<td>ENGAGE AF-TIMI48</td>
<td>NEJM 2013; 369:2093-2104</td>
<td>AF patients treated with edoxaban had similar rates of stroke and lower rates of major bleeding compared to warfarin</td>
</tr>
<tr>
<td>RE-LY</td>
<td>NEJM 2009; 361:1139-51</td>
<td>AF patients treated with dabigatran had a lower incidence of stroke compared to warfarin, with similar rates of major bleeding</td>
</tr>
<tr>
<td>ROCKET-AF</td>
<td>NEJM 2011; 365:983-891</td>
<td>In patients with AFib rivoxabarin is non-inferior to warfarin for stroke prevention, and major and non-major bleeding</td>
</tr>
<tr>
<td>HYPERTENSION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYVET</td>
<td>NEJM 2008; 358:1887-98</td>
<td>In hypertensive patients &gt;80 yr treatment with indapamide, with or without perindopril, showed a trend towards reduced relative risk of fatal or non-fatal stroke</td>
</tr>
<tr>
<td>SIPLICITY-HTN 3</td>
<td>NEJM 2014; 370:1393-1401</td>
<td>Renal denervation does not reduce blood pressure in patients with resistant hypertension compared to sham procedure</td>
</tr>
<tr>
<td>UKHDS (UKPDS)</td>
<td>BMJ 1998; 317:703-13</td>
<td>Hypertensive patients with DM and tight BP control at &lt;150/85 mmHg by use of ACEI or β-blocker reduced risk of diabetic complications and death related to DM and reduced risk of end-organ damage</td>
</tr>
<tr>
<td>VALUE</td>
<td>Lancet 2004; 363:2022-2031</td>
<td>Valsartan group had higher incidence of MI than amlodipine group, whereas amlodipine had a higher incidence of new-onset DM</td>
</tr>
</tbody>
</table>
Cath/EP
Hayes D, Forman S. Cardiac pacing: how it started, where we are, where we are going. J Cardiovasc Electrophysiol 2004;15:619-627.

Arrhythmias

Percutaneous Angiography/PCI

Cardiovascular Surgery
General Principles

Drug Nomenclature

- **chemical name**: describes chemical structure; consistent in all countries (e.g. \(N\)-(4-hydroxyphenyl)acetamide is acetaminophen)
- **DIN** or **NDC**: DIN assigned by Health Canada; NDC assigned by FDA (US)
- **non-proprietary name**: approved name (post-phase III trial), official name (listed in pharmacopoeia), or generic name (off-patent) (e.g. acetaminophen)
- **proprietary (trade) name**: the brand name or registered trademark (e.g. Tylenol®)

**Phases of Clinical Drug Testing**

- **phase I**: first administration to healthy human volunteers, following animal studies; to determine PK and PD
- **phase II**: first administration to patients, small sample sizes; to determine initial safety and efficacy, dose range, PK, and PD
- **phase III**: large sample sizes, often double-blinded RCT; comparative (new drug vs. placebo or standard of care) to establish safety and efficacy
- **phase IV**: post-marketing surveillance, wide distribution; to determine effects of long-term use, rare ADRs, ideal dosing, and effects in real-world practice

**Drug Administration**

- choice of route of administration depends on: drug properties, local and systemic effects, desired onset and/or duration of action, and patient characteristics

**Table 1. Routes of Drug Administration**

<table>
<thead>
<tr>
<th>Route</th>
<th>Advantage</th>
<th>Disadvantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral (PO)</td>
<td>Convenient, easy to administer</td>
<td>Incomplete absorption</td>
</tr>
<tr>
<td></td>
<td>Large surface area for absorption</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inexpensive relative to parenteral administration</td>
<td></td>
</tr>
<tr>
<td>Buccal/Sublingual (SL)</td>
<td>Rapid onset of action</td>
<td>Must be lipid-soluble, non-irritating</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Short duration of action</td>
</tr>
<tr>
<td>Rectal (PR)</td>
<td>Almost no hepatic first-pass effect</td>
<td>Inconvenient, irritation at site of application</td>
</tr>
<tr>
<td></td>
<td>Use when NPQ, vomiting, or unconscious</td>
<td>Erratic absorption</td>
</tr>
<tr>
<td>Intravenous (IV)</td>
<td>No hepatic first-pass effect</td>
<td>Hard to remove once administered</td>
</tr>
<tr>
<td></td>
<td>Slow infusion or rapid onset of action</td>
<td>Risk of infection, bleeding, vascular injury</td>
</tr>
<tr>
<td></td>
<td>Easy to titrate dose</td>
<td>Extravasation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td>Intramuscular (IM)</td>
<td>Depot storage if oil-based = slow release of drug</td>
<td>Pain/hematoma at site of injection</td>
</tr>
<tr>
<td></td>
<td>Aqueous solution = rapid onset of action</td>
<td></td>
</tr>
<tr>
<td>Subcutaneous (SC)</td>
<td>Non-irritating drugs, small volumes</td>
<td>Pain at site of injection</td>
</tr>
<tr>
<td></td>
<td>Constant, even absorption</td>
<td>Smaller volumes than IM</td>
</tr>
<tr>
<td></td>
<td>Alternative to IV</td>
<td>May have tissue damage from multiple injections</td>
</tr>
<tr>
<td>Intrathecal</td>
<td>Direct into CSF</td>
<td>Risk of infection</td>
</tr>
<tr>
<td>Inhalation</td>
<td>Immediate action in lungs</td>
<td>Must be gas, vapour, or aerosol</td>
</tr>
<tr>
<td>Topical</td>
<td>Easy to administer</td>
<td>Effects are mainly limited to site of application</td>
</tr>
<tr>
<td></td>
<td>Localized (limited systemic absorption)</td>
<td></td>
</tr>
<tr>
<td>Transdermal</td>
<td>Drug absorption through intact skin</td>
<td>Iritation at site of application</td>
</tr>
<tr>
<td></td>
<td>No hepatic first-pass effect</td>
<td>Delayed onset of action</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hydrophilic drugs not easily absorbed</td>
</tr>
<tr>
<td>Others (intraperitoneal, intra-articular)</td>
<td>Local effect</td>
<td>Risk of infection</td>
</tr>
</tbody>
</table>

**Common Latin Abbreviations**

- q each, every
- OD/bid/tid/qid once/twice/three/four times a day
- hs at bedtime
- ac/po/cc before/after/with meals
- prn as necessary
- gtt drops
- ung ointment
- ud as directed
- od/os/ou right/left/each eye
- ad/as/ae right/left/each ear

At the time of drug launch, only data from phases I-III are available; thus, effectiveness and safety may be unknown because real-world patients and usage patterns often differ from those in premarket phases.
Pharmacokinetics

- study of “what the body does to a drug”
- definition: relationship between drug administration, time-course/rate of absorption and distribution, concentration changes in the body compartments, and the drug’s removal from the body

Absorption

- definition: movement of the drug from the site of administration into plasma

Mechanisms of Drug Absorption

- most drugs are absorbed into the systemic circulation via passive diffusion
- other mechanisms: active transport, facilitated diffusion, and pinocytosis/phagocytosis

Factors Affecting the Rate and Extent of Drug Absorption

- \( P_{o/w} \) (i.e. its relative solubility in oil (lipid) vs. water)
- local blood flow at the site of administration (e.g. sublingual vessels facilitate rapid absorption of SL medications)
- molecular size (e.g. small molecular weight drugs absorb faster)
- \( \text{pH and drug ionization} \)
  - drugs are usually weak acids (e.g. ASA) or weak bases (e.g. ketoconazole) and thus exist in ionized and non-ionized forms
  - body compartment \( \text{pH} \) and drug \( \text{pK}_a \) determine the ratio of ionized to non-ionized drug molecules (using the Henderson-Hasselbach equation)
  - non-ionized forms cross cell membranes much faster than ionized (charged) forms
- total surface area for absorption
  - small intestinal villi are the primary site of absorption for most oral drugs

Bioavailability (F)

- definition: proportion of dose that reaches systemic circulation in an unchanged state
- decreased by: limited drug absorption or gut metabolism and hepatic first-pass effect
- IV dose has 100% bioavailability (\( F = 1 \))

First-Pass Effect

- definition: drug metabolism by the liver and sometimes the gut before it reaches systemic circulation, resulting in reduced F
- occurs with PO administration of a drug: GI tract (absorption) → portal vein to liver (first-pass metabolism) → systemic circulation
- occurs to a much lesser extent with PR administration because drug absorbed in colon bypasses the portal system: colon (absorption) → internal pudendal veins → IVC → systemic circulation

Efflux Pump

- Pgp is a protein in the GI tract, renal epithelium, and elsewhere that acts as a multidrug efflux pump involved in the transport of drugs out of cells
- opposes intestinal absorption and enhances renal elimination of certain drugs (e.g. digoxin, dabigatran, etoposide, paclitaxel, tacrolimus, cyclosporine)
- some drugs (e.g. macrolide antibiotics) inhibit Pgp function, leading to increased levels of Pgp substrates; Pgp inducers (e.g. St. John’s wort) do the opposite
- some tumours overexpress Pgp leading to multidrug resistance to chemotherapy agents

Distribution

- definition: movement of drugs between different body compartments and to the site of action
- major body fluid compartments: plasma, interstitial fluid, intracellular fluid, transcellular fluid (e.g. CSF, peritoneal, pleural)
- tissue compartments: fat, brain

Factors Affecting the Rate and Extent of Drug Distribution

- physiochemical properties of the drug (e.g. \( P_{o/w} \) and \( \text{pK}_a \))
- \( \text{pH} \) of fluid
- plasma protein binding
- binding within compartments (i.e. depots)
- regional blood flow

**Figure 1. Distribution of total body water (TBW)**
Volume of Distribution
- maximum actual V_d (anatomic fluid volume accessible to drug) = TBW (TBW~40 L for average adult)
- V_d: the apparent volume of fluid into which a drug distributes
  - a calculated value = amount of drug in body ÷ plasma drug concentration
  - a theoretical value that does not correspond to an anatomical space (i.e. can exceed TBW)
  - a calculated V_d of a drug that concentrates in plasma and/or binds plasma proteins to a high degree
  - large V_d corresponds to a drug that distributes into tissues (fat, muscle, etc.); most is not in blood (measured) space, and it therefore appears to distribute in a large volume
  - V_d of plasma-protein bound drugs can be altered by liver and kidney disease
- example: amiodarone distributes into TBW (actual V_d = 40 L), but it also concentrates in fat tissues giving instead an apparent V_d of 400 L; therefore, to achieve a given plasma concentration of amiodarone, we dose as though the drug distributes into 400 L of body fluid

Plasma Protein Binding
- drug molecules in the blood exist in an equilibrium of two forms:
  1. bound to plasma protein: acidic drugs bind to albumin, basic drugs bind to α1-acid glycoprotein
  2. free or unbound: can leave the circulation to distribute into tissues and exert an effect, subject to metabolism and elimination
- bound fraction is determined by drug concentration, binding affinity, and plasma protein concentration (number of binding sites)
- reduced number of binding sites (e.g. hypoalbuminemia) or saturation of binding sites (e.g. competition/displacement) may result in increased concentration of free drug, which is often metabolized with no harmful effects, although toxicity is possible

Depots
- a body compartment in which drug molecules tend to be stored and released slowly over a long period of time
- fat is a depot for very lipid soluble drugs (e.g. diazepam)
- some oil-based medications are injected IM for slow release (e.g. depot medroxyprogesterone acetate q3mo; depot risperidone q2wk)

Barriers (relative)
- body structures that limit or prevent diffusion of drug molecules, such as the placenta or BBB (a barrier composed of tight junctions between capillary endothelial cells and astrocytes)
- many of these barriers result, in part, from the activity of multidrug efflux pumps (e.g. Pgp), which serve as a natural defense mechanism against drugs and xenobiotics
- need to consider dosing route if drugs are meant to cross these barriers

Metabolism (Biotransformation)
- definition: chemical transformation of a drug in vivo to enhance elimination
- sites of biotransformation: liver (main), GI tract, lung, plasma, kidney
- as a result of the process of biotransformation:
  - an inactive prodru may be activated (e.g. tamoxifen to endoxifen; codeine to morphine)
  - a drug may be changed to another active metabolite (e.g. diazepam to oxazepam)
  - a drug may be changed to a toxic metabolite (e.g. meperidine to normeperidine)
  - a drug may be inactivated (most drugs)

Drug Metabolizing Pathways
- phase I (P450) reactions
  - minor molecular changes introduce or unmask polar groups on a parent compound to increase water solubility (e.g. oxidation-reduction, hydrolysis, hydroxylation); the change in P=0 is typically minimal compared to phase II, and often phase I places a polar ‘handle’ on a lipophilic drug to allow for phase II
  - mediated by CYPs found in the endoplasmic reticulum
  - product of the reaction can be excreted or undergo further phase II reactions
- phase II (conjugation) reactions
  - conjugation with large polar endogenous substrates (e.g. glucuronidation, glutathione conjugation, sulfation)
  - dramatically increases water solubility and renal elimination
  - can result in biologically active metabolites (e.g. glucuronides of morphine)
  - can occur independently of phase I reactions
Factors Affecting Drug Biotransformation

- genetic polymorphisms of metabolizing enzymes
  - individual genotypes may determine rate of drug metabolism (e.g. poor, intermediate, extensive, or ultrarapid metabolizers)
  - may lead to toxicity or ineffectiveness of a drug at a normal dose
    - tamoxifen and codeine are prodrugs activated by CYP2D6 (nonfunctional alleles reduce effectiveness, whereas overactive/duplicated alleles impart “ultra-rapid metabolizer” phenotype)
    - warfarin is metabolized by CYP2C9 (nonfunctional alleles lead to greater effect and lower dose requirements)
- enzyme inhibition may sometimes be due to other drugs
  - CYP inhibition leads to an increased concentration and bioavailability of the substrate drug (e.g. erythromycin [CYP3A4 inhibitor], can predispose patients to simvastatin toxicity [metabolized by CYP3A4])
- enzyme induction
  - certain medications enhance gene transcription leading to an increase in the activity of a metabolizing enzyme
  - a drug may induce its own metabolism (e.g. carbamazepine) or that of other drugs (e.g. phenobarbital can induce the metabolism of OCPs) by inducing the CYP system
- liver dysfunction (e.g. hepatitis, alcoholic liver, biliary cirrhosis, or hepatocellular carcinoma) may decrease drug metabolism but this may not be clinically significant due to the liver's reserve capacity
- renal disease often results in decreased drug clearance
- extremes of age (neonates or elderly) have reduced biotransformation capacity, and doses should be adjusted accordingly
- nutrition: insufficient protein and fatty acid intake decreases CYP biotransformation, and vitamin/mineral deficiencies may also impact other metabolizing enzymes
- alcohol: while acute alcohol ingestion inhibits CYP2E1, chronic consumption can induce CYP2E1 and increase risk of hepatocellular damage from acetaminophen by increasing the generation of acetaminophen's toxic metabolite
- smoking can induce CYP1A2, thus increasing the metabolism of some drugs (e.g. theophylline, antipsychotic)

Elimination

- definition: removal of drug from the body

Routes of Drug Elimination

- kidney (main organ of elimination): two mechanisms
  1. glomerular filtration
     - a passive process, so that only the free drug fraction can be eliminated
     - drug filtration rate depends on GFR, degree of protein binding of drug, and size of drug
  2. tubular secretion
     - an active process that is saturable allowing both protein-bound and free drug fractions to be excreted
     - distinct transport mechanisms for weak acids (e.g. penicillin, salicylic acid, probenecid, chlorothiazide) and weak bases (e.g. quinine, quaternary ammonium compounds such as choline)
     - drugs may competitively block mutual secretion if both use the same secretion system (e.g. probenecid can reduce the excretion of penicillin)

- tubular reabsorption: drugs can be passively reabsorbed back to the systemic circulation, countering elimination mechanisms
- renal function (decreases with age and is affected by many disease states) is assessed clinically using serum Cr levels
- stool: some drugs and metabolites are actively excreted in the bile or directly into the GI tract
- enterohepatic reabsorption counteracts stool elimination, and can prolong the drug's duration in the body
  - some glucuronide conjugates that are excreted in bile may be hydrolyzed in the intestines by bacteria back to their original form and can be systemically reabsorbed
- lungs: elimination of anesthetic gases and vapours by exhalation
- saliva: saliva concentrations of some drugs parallel their plasma levels (e.g. rifampin)
Pharmacokinetic Calculation

- definition: the quantitative description of the rates of the various steps of drug disposition (i.e. how drugs move through the body)
- the pharmacokinetic principles of ADME (absorption, distribution, metabolism, and elimination) can be graphically represented on a concentration vs. time graph

Time Course of Drug Action
- many kinetic parameters are measured using IV dosing, such that absorption is immediate and distribution for most drugs is rapid; thus elimination is the main process being measured
- the concentration axis is converted to a log10 concentration to allow for easier mathematical calculations
- drugs such as warfarin can exhibit hysteresis where a delayed pharmacological response results from a series of biological events upon the drug interacting with a specific receptor at the effect site

Half-Life
- definition: time taken for the serum drug level to fall 50% during elimination
- drugs with first order kinetics require five half-lives to reach steady state with repeated dosing or for complete drug elimination once dosing is stopped

<table>
<thead>
<tr>
<th># of Half-Lives</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>3.3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of Steady State Concentration</td>
<td>50</td>
<td>75</td>
<td>87.5</td>
<td>90</td>
<td>93.8</td>
<td>96.9</td>
</tr>
</tbody>
</table>

Steady State
- drug concentration remains constant when amount of drug entering the system is eliminated from the system
- appropriate timing is important for therapeutic monitoring since drug levels are reliable only when the drug has reached steady state
- special situations
  - use a loading dose for drugs with a long half-life and when there is clinical need to rapidly achieve therapeutic levels (e.g. amiodarone, digoxin, phenytoin)
  - use continuous infusion for drugs with a very short half-life and when there is need for a long-term effect or multiple or frequently repeated doses are too inconvenient (e.g. nitroprusside, insulin, unfractionated heparin)

Clearance
- a quantitative measurement of the body fluid volume from which a substance is removed per unit time
- CI = rate of elimination of drug / plasma drug concentration
- must consider CI from a specific part of the body and total body CI

Elimination Kinetics
- first-order kinetics (most common type)
  - constant fraction of drug eliminated per unit time
  - some drugs can follow first-order kinetics until elimination is saturated (usually at large doses) at which point the CI decreases
  - becomes linear relationship when plotted on a log(concentration) vs. time graph
- zero-order kinetics (less common, associated with overdose, e.g. alcohol)
  - a constant rate of drug eliminated regardless of concentration; concept of half-life does not apply
  - the concentration axis is converted to a log (concentration) to allow for easier mathematical calculations

Table 2. Loading vs. Maintenance Dosing

<table>
<thead>
<tr>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use when you need an IMMEDIATE effect</td>
<td>After a loading dose OR beginning with maintenance doses</td>
</tr>
<tr>
<td>Often parenteral medication</td>
<td>Steady-state levels achieved after ~5 half-lives</td>
</tr>
<tr>
<td>Rationale: give large dose of medication to “fill up” the volume of distribution</td>
<td>Can be given as either a continuous infusion (relatively rare, short half-life drug) OR much more commonly as intermittent doses</td>
</tr>
</tbody>
</table>

Figure 2. Time course of drug action
For most drugs it takes 5 half-lives to reach steady state with repeated dosing or to eliminate a drug once dosing is stopped

Figure 3. Steady state of a drug displaying first-order kinetics
Steady state of a drug with t1/2 of 3 h. It takes about 15 h (5 x t1/2) to reach steady state.

Dosing interval = 6 h

Steady State at 5 t1/2

Figure 4. First and zero order kinetics
In first order kinetics (solid line), a constant fraction of the drug is eliminated per unit time; in zero order kinetics (dashed line), a constant amount of the drug is eliminated per unit time

Principles of Pharmacokinetics
- $V_d =$ amount of drug in the body / plasma drug concentration
- $Cl =$ rate of elimination of drug/plasma drug concentration
- $Half-life (t_{1/2}) = \frac{0.7xV_d}{Cl}$
Pharmacodynamics

• study of “what the drug does to the body”

Dose-Response Relationship

• graded dose-response relationships: relates dose to intensity of effect

Efficacy

• the maximum biological response produced by a drug
• measured by $E_{\text{max}}$ (the maximal response that a drug can elicit in a RCT or under optimal circumstances)

Potency

• measured by $EC_{50}$ (the concentration of a drug needed to produce 50% of $E_{\text{max}}$)
• a drug that reaches its $EC_{50}$ at a lower dose is more potent

Efficacy vs. Potency

• Efficacy measures the maximal effect of a drug
• Potency measures the concentration of a drug needed to produce a certain effect

Effects of Drugs on Receptors

Agonists

• drugs that mimic the effects of the endogenous ligand and evoke a response when bound to the receptor
  ▪ affinity: the ability of the agonist to bind to the receptor (e.g. the $\beta_2$-agonist salbutamol has greater affinity for $\beta_2$-receptors than $\beta_1$-receptors)
  ▪ efficacy: the ability to recapitulate endogenous response via the receptor interaction (e.g. binding of salbutamol to $\beta_2$-receptors results in smooth muscle relaxation)
• full agonists: can elicit a maximal effect at a receptor
• partial agonists: can only elicit a partial effect, no matter the concentration at the receptor (i.e. reduced efficacy compared to full agonists) (e.g. varenicline is a partial agonist of the $\alpha_4\beta_2$ nicotinic receptor)

Antagonists

• drugs that block the action of an agonist or of an endogenous ligand
• chemical antagonism: direct chemical interaction between agonist and antagonist prevents agonist-receptor binding (e.g. chelating agents for removal of heavy metals)
• functional antagonism: two agonists that act independently at different receptors and have opposite physiological effects (e.g. acetylcholine at the muscarinic receptor compared to epinephrine at the adrenergic receptor)
• reversible and irreversible competitive antagonism
  ▪ drugs that have affinity but no efficacy for their cognate receptors, and therefore, exert no effect upon binding
  ▪ reversible competitive antagonists reversibly bind to the same receptor as the agonist, thus displacing it (e.g. naloxone is an antagonist to morphine or heroin)
  ▪ irreversible antagonists irreversibly bind to the same receptor as the agonist, blocking it from binding (e.g. phenoxybenzamine forms a covalent bond with adrenergic receptors preventing adrenaline and NE from binding)
• non-competitive antagonism
  ▪ antagonist binds to an alternate site near the agonist site, producing allosteric effects that change the ability of the agonist to bind (e.g. organophosphates irreversibly bind acetylcholinesterase)
Figure 8. Mechanism of agonists and antagonists

Effectiveness and Safety

Effectiveness
- ED\textsubscript{50} (effective dose): the dose of a drug needed to cause a therapeutic effect in 50% of a test population of subjects

Safety
- LD\textsubscript{50} (lethal dose): the dose of a drug needed to cause death in 50% of a test population of subjects
- TD\textsubscript{50} (toxic dose): the dose needed to cause a harmful effect in 50% of a test population of subjects

Therapeutic Indices

Therapeutic Index: TD\textsubscript{50}/ED\textsubscript{50}
- reflects the “margin of safety” for a drug – the likelihood of a therapeutic dose to cause serious toxicity or death
- the larger the TI, the safer a drug (e.g. warfarin has a narrow TI and require drug monitoring)
- factors that can change the TI
  - presence of interacting drugs
  - changes in drug ADME

Certain Safety Factor: TD\textsubscript{1}/ED\textsubscript{99}
- >1 translates to a dose effective in at least 99% of the population and toxic in less than 1% of the population
Therapeutic Drug Monitoring

- **definition**: using serum drug concentration data to optimize drug therapy (e.g. dose adjustment, monitor compliance)
  - serum drug samples are usually taken when the drug has reached steady state (after approximately 5 half-lives)
  - TDM is often used for drugs that have: narrow TIs, unpredictable dose-response relationships, significant consequences associated with therapeutic failure or toxicity, and wide inter-patient pharmacokinetic variability

Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Definition</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (Augmented)</td>
<td>Dose related</td>
<td>• Predictable extension of drug’s pharmacologic effect (e.g. &amp;-blockers causing bradycardia) • &gt;80% of all ADRs</td>
</tr>
<tr>
<td>B (Bizarre)</td>
<td>Non-dose related</td>
<td>• Reactions unrelated to the known pharmacological actions of the drug • Examples include: drug hypersensitivity syndromes, immunologic reactions (penicillin hypersensitivity), and idiosyncratic reactions (malignant hyperthermia)</td>
</tr>
<tr>
<td>C (Chronic)</td>
<td>Dose and time related</td>
<td>• Related to cumulative doses • Effects are well-known and can be anticipated (e.g. atypical femoral fracture from bisphosphonates)</td>
</tr>
<tr>
<td>D (Delayed)</td>
<td>Time related</td>
<td>• Occurs some time after use of drug (e.g. carcinogen) • May also be dose-related</td>
</tr>
<tr>
<td>E (End of use)</td>
<td>Withdrawal</td>
<td>• Occurs after cessation of drug use (e.g. opiate withdrawal)</td>
</tr>
</tbody>
</table>

Approach to Suspected Adverse Drug Reactions

- history and physical exam: signs and symptoms of reaction (e.g. rash, fever, hepatitis, anaphylaxis), timing, risk factors, detailed medication history including all drugs and timing, de-challenge (response when drug is removed), and re-challenge (response when drug is given again)
- differentiate between drug therapy vs. disease pathophysiology
- treatment: stop the drug, supportive care, symptomatic relief
- resources: check recent literature, Health Canada, and FDA; contact the pharmaceutical company; call Poison Control (1-888-268-9017) if overdose or poisoning suspected; check with Motherisk (www.motherisk.org) in cases involving pregnant or breastfeeding women
- report all suspected ADRs that are: 1) unexpected, 2) serious, or 3) reactions to recently marketed drugs (on the market <5 yr) regardless of nature or severity
- Canadian Adverse Drug Reaction Monitoring Program available for online reporting

Examples of drugs whose levels need to be monitored: warfarin (via INR levels), digoxin, lithium, anti-epileptics (e.g. phenytoin, carbamazepine)

Sample of Clinically Relevant Adverse Drug Reactions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Drug(s)</th>
<th>ADR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>&amp;-blockers</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>A</td>
<td>ACEIs</td>
<td>Cough</td>
</tr>
<tr>
<td>A</td>
<td>NSAIDs</td>
<td>GI bleeding</td>
</tr>
<tr>
<td>A</td>
<td>Opiates</td>
<td>GI upset, constipation, urinary retention, respiratory depression</td>
</tr>
<tr>
<td>A</td>
<td>Acetaminophen</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>A</td>
<td>Vancomycin</td>
<td>Red Man syndrome</td>
</tr>
<tr>
<td>A</td>
<td>Aminoglycosides</td>
<td>Ototoxicity and nephrotoxicity</td>
</tr>
<tr>
<td>B</td>
<td>Sulfonamides</td>
<td>Stevens-Johnson syndrome, Toxic epidermal necrolysis</td>
</tr>
<tr>
<td>B</td>
<td>Penicillins</td>
<td>Rash</td>
</tr>
<tr>
<td>B</td>
<td>Valproic acid, Chinese herbs</td>
<td>Hepatotoxicity</td>
</tr>
</tbody>
</table>
Variability in Drug Response

• recommended patient dosing is based on clinical research and represents mean values for a select population, but each person may be unique in their dosing requirements
• possible causes of individual variability in drug response include problems with:
  ♦ intake: patient adherence
  ♦ pharmacokinetics
    – absorption: vomiting, diarrhea, or steatorrhea; first pass effect increased due to enzyme induction or decreased due to liver disease
    – drug interactions (e.g. calcium carbonate complexes with iron, thyroxine, and fluoroquinolones)
    – distribution: very high or low percentage body fat; intact or disrupted BBB; patient is elderly or a neonate, or has liver dysfunction
    – biotransformation and elimination: certain genetic polymorphisms or enzyme deficiencies related to drug metabolism (e.g. acetylcholinesterase deficiency, CYP polymorphism); kidney or liver dysfunction
  ♦ pharmacodynamics: genetic variability in drug response (e.g. immune-mediated reactions); diseases that affect drug pharmacodynamics; drug tolerance or cross-tolerance

Drug Interactions

• concomitant prescriptions: one drug alters the effect of another by changing its PK and/or PD
• PK interactions involve changes in drug concentration
  ▪ absorption: alterations in gastrointestinal pH, gastric emptying, intestinal motility, gut mucosal function
  ▪ biotransformation: alterations in drug metabolizing enzymes
  ▪ excretion: alterations in renal elimination
• PD interactions are due to two drugs that exert similar effects (additive) or opposing effects (subtractive)
• drug interactions can also involve herbal medications (e.g. St. John’s wort) and food (e.g. grapefruit)

Autonomic Pharmacology

Figure 10. Subdivisions of the peripheral nervous system

• the autonomic nervous system is divided into sympathetic and parasympathetic divisions
• most organs are innervated by both sympathetic and parasympathetic nerves, which have opposing effects (see Neurology, N8)
• ACh and NE are the main neurotransmitters of the autonomic NS
• ACh binds to cholinergic receptors, which include nicotinic and muscarinic receptors
• NE binds to adrenergic receptors, which principally include β1, β2, α1, and α2
• ACh action is terminated by metabolism in the synaptic cleft by acetylcholinesterase and in the plasma by pseudocholinesterase
• acetylcholinesterase inhibitors (pyridostigmine, donepezil, galantamine, rivastigmine) can be used to increase ACh levels in conditions such as myasthenia gravis or Alzheimer’s disease
• NE action is terminated by reuptake by the presynaptic membrane, diffusion from the synaptic cleft, and degradation by monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT)
Parasympathetic Nervous System

- blood vessels, adrenals, sweat glands, spleen capsule, and adrenal medulla do NOT have parasympathetic innervation
- parasympathetic pre-ganglionic fibres originate in the lower brainstem from cranial nerves III, VII, IX, X, and in the sacral spinal cord at levels S2-S4 and connect with post-ganglionic fibres via nicotinic receptors in ganglionic cells located near or within the target organ
- post-ganglionic fibres connect with effector tissues via:
  - $M_1$ muscarinic receptors located in the CNS
  - $M_2$ muscarinic receptors located in smooth muscle, cardiac muscle, and glandular epithelium

Sympathetic Nervous System

- sympathetic pre-ganglionic fibres originate in the spinal cord at spinal levels T1-L3
- pre-ganglionic fibres connect with post-ganglionic fibres via nicotinic receptors located in one of two groups of ganglia
  1. paravertebral ganglia (i.e. the sympathetic trunk) that lie in a chain close to the vertebral column
  2. pre-vertebral ganglia (i.e. celiac and mesenteric ganglia) that lie within the abdomen
- post-ganglionic fibres connect with effector tissues via
  - $\beta_1$ receptors in cardiac tissue
  - $\beta_2$ receptors in smooth muscle of bronchi and GI tract
  - $\alpha_1$ receptors in vascular smooth muscle
  - $\alpha_2$ receptors in vascular smooth muscle
  - $M_3$ muscarinic receptors located in sweat glands

Table 4. Direct Effects of Autonomic Innervation on the Cardiorespiratory System

<table>
<thead>
<tr>
<th>Organ</th>
<th>Sympathetic NS</th>
<th>Parasympathetic NS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Receptor/Action</td>
<td>Receptor/Action</td>
</tr>
<tr>
<td>Heart</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Sinoatrial</td>
<td>$\beta_1$ Increased HR</td>
<td>$M$ Decreased conduction</td>
</tr>
<tr>
<td>2. Atrioventricular node</td>
<td>$\beta_1$ Increased conduction</td>
<td>$M$ Decreased conduction</td>
</tr>
<tr>
<td>3. Atria</td>
<td>$\beta_1$ Increased contractility</td>
<td>$M$ Decreased conduction</td>
</tr>
<tr>
<td>4. Ventricles</td>
<td>$\beta_1$ Increased contractility</td>
<td>$M$ Decreased HR</td>
</tr>
<tr>
<td>Blood Vessels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Skin, splanchnic</td>
<td>$\alpha_1, \alpha_2$ Constriction</td>
<td>$M$ Dilatation</td>
</tr>
<tr>
<td>2. Skeletal muscle</td>
<td>$\alpha$ Constriction</td>
<td>$M$ Dilatation</td>
</tr>
<tr>
<td>3. Coronary</td>
<td>$\beta_2$ (large muscles) Dilatation</td>
<td>$M$ Dilatation</td>
</tr>
<tr>
<td>Lungs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Bronchiolar smooth muscle</td>
<td>$\beta_2$ Relaxation</td>
<td>$M$ Constriction</td>
</tr>
<tr>
<td>2. Bronchiolar glands</td>
<td>$\alpha_1, \beta_2$ Increased secretion</td>
<td>$M$ Stimulation</td>
</tr>
</tbody>
</table>
### Common Drug Endings

#### Table 5. Common Drug Endings

<table>
<thead>
<tr>
<th>Ending</th>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>-afil</td>
<td>5-PDE inhibitor</td>
<td>sildenafil</td>
</tr>
<tr>
<td>-ane</td>
<td>Inhaled general anesthetic</td>
<td>halothane</td>
</tr>
<tr>
<td>-azepam</td>
<td>Benzodiazepine</td>
<td>lorazepam</td>
</tr>
<tr>
<td>-azole</td>
<td>Antifungal</td>
<td>ketoconazole</td>
</tr>
<tr>
<td>-caine</td>
<td>Local anesthetic</td>
<td>lidocaine</td>
</tr>
<tr>
<td>-olol</td>
<td>β-blocker</td>
<td>propranolol</td>
</tr>
<tr>
<td>-prazole</td>
<td>Proton pump inhibitor</td>
<td>omeprazole</td>
</tr>
<tr>
<td>-pril</td>
<td>ACE inhibitor</td>
<td>captopril</td>
</tr>
<tr>
<td>-sartan</td>
<td>ARB</td>
<td>candesartan</td>
</tr>
<tr>
<td>-statin</td>
<td>HMG-CoA inhibitor</td>
<td>atorvastatin</td>
</tr>
<tr>
<td>-terol</td>
<td>β2 agonist</td>
<td>albuterol</td>
</tr>
<tr>
<td>-tidine</td>
<td>H2 antagonist</td>
<td>cimetidine</td>
</tr>
<tr>
<td>-tropin</td>
<td>Pituitary hormone</td>
<td>somatotropin</td>
</tr>
<tr>
<td>-vir</td>
<td>Antiviral</td>
<td>acyclovir</td>
</tr>
<tr>
<td>-zisin</td>
<td>α1 antagonist</td>
<td>prazosin</td>
</tr>
</tbody>
</table>

Note: Some medications are exceptions to the rule, e.g. methimazole (antithyroid)

### References

**Principles of Clinical Pharmacology**

**Adverse Drug Reactions**

**Drug Interactions**
Dermatology

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Scarring (Cicatricial) Alopecia

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Introduction to Skin

Skin Anatomy

Figure 1. Histologic layers of the skin. Epidermal layer is detailed in A

- Epidermis
  - avascular: receives its nutrition from the dermal capillaries
  - derived from keratinocytes with the youngest presenting at the stratum basale
  - cells progress from stratum basale to stratum corneum in about 4 wk
    - stratum basale (germinativum): mitotic figures that give rise to keratinocytes
    - stratum spinosum (prickle cells): junctions in this layer (tonofilaments) give the epidermis its strength
    - stratum granulosum: flat cells containing basophilic granules which characterize skin
    - stratum lucidum: comprised of transparent layers of packed dead cells
    - stratum corneum: flat scales of the water-resistant protein keratin
  - cells of the epidermis
    - keratinocytes: located in all layers of the epidermis, except the stratum corneum; connected to each other by desmosomes
    - melanocytes: located in the stratum basale; keratinocyte to melanocyte ratio in the basal layer is 10:1; melanocyte number is equal among races; produces melanosomes containing melanin, which are transferred to keratinocytes
    - Merkel cells: located in the basal layer; involved in touch sensation
  - dermis: comprised of connective tissue divided into two regions
    - papillary: contains numerous capillaries that supply nutrients to the dermis and epidermis
    - reticular: provides a strong structure for skin; consists of collagen bundles woven together along with elastic fibres, fibroblasts, and macrophages
    - cells of dermis
    - fibroblasts: produces collagen, elastin, and ground substance
    - mast cells: releases histamines which mediate type I hypersensitivity
- Subcutaneous tissue (subdermal)
  - consists primarily of adipose cells, larger caliber vessels, nerves and fascia

Epidermal Appendages
- epidermal in origin, can extend into the dermis; includes hair, nails, and cutaneous glands
- pilosebaceous unit = hair + hair follicle + sebaceous gland + arrector pili muscle

Cutaneous Glands
- sebaceous gland: part of pilosebaceous unit, produces sebum which is secreted into the hair follicle via the sebaceous duct, where it covers the skin surface (protective function)
  - sebum has some antifungal properties
  - these glands cover entire skin surface and are absent only in non-hair bearing areas (e.g. palms, soles, lips)
- apocrine sweat gland: apocrine duct empties into hair follicle above sebaceous gland
  - found in axillae and perineum
  - likely a vestigial structure, functions in other species to produce scent (e.g. pheromones)
- eccrine sweat gland: not part of pilosebaceous unit
  - found over entire skin surface except lips, nail beds, and glans penis
  - important in temperature regulation via secretion of sweat to cool skin surface

Acronyms

- hCG: human chorionic gonadotropin
- AAFP: American Academy of Family Physicians
- AD: atopic dermatitis
- AK: actinic keratosis
- AS: anti-Streptolysin O
- BCC: basal cell carcinoma
- BSA: body surface area
- Brun: blood urea nitrogen
- CBC: complete blood count
- CMV: cytomegalovirus
- CNS: central nervous system
- Cr: creatinine
- CXR: chest x-ray
- DLE: discoid lupus erythematosus
- DM: diabetes mellitus
- DVT: deep vein thrombosis
- EM: erythema multiforme
- Fe: iron
- FTA-ABS: fluorescent treponemal antibody-absorption test
- GAS: group A beta-hemolytic Streptococcus
- GVRD: graft-versus-host disease
- HHV: human herpes virus
- HIPA: hypopituitary-adrenal
- HPV: human papillomavirus
- HRT: hormone replacement therapy
- HSV: herpes simplex virus
- HDV: herpes zoster virus
- IFN: interferon
- IVlg: intravenous immunoglobulin
- IFT: liver function test
- MADD: monamine oxidase inhibitor
- MM: malignant melanoma
- MMR: measles/mumps/rubella
- MRSA: methicillin-resistant Staphylococcus aureus
- MTP: metatarsal phalangeal
- NB-UVB: narrow band ultraviolet wavelength B
- NCT: neocellular neus
- Nd:Yag: neodymium-doped yttrium aluminum garnet
- NNM: neovernelanocytic neus
- NMSC: nonmelanoma skin cancers
- NSAAID: nonsteroidal anti-inflammatory drug
- OCP: oral contraceptive pill
- OTC: over-the-counter
- PABA: para-aminobenzoic acid
- PASI: Psoriasis Area and Severity Index
- PPD: purified protein derivative
- PUVA: psoralens and long wave ultraviolet radiation
- RA: rheumatoid arthritis
- SCC: squamous cell carcinoma
- SHBG: sex hormone-binding globulin
- SJS: Stevens-Johnson syndrome
- SLE: systemic lupus erythematosus
- SPF: sun protection factor
- SSG: selective serotonin reuptake inhibitor
- SSSS: staphylococcal scalded skin syndrome
- STI: sexually transmitted infection
- TB: tuberculosis
- TEN: toxic epidermal necrolysis
- TMP/SMX: trimethoprim-sulfamethoxazole
- TSH: thyroid stimulating hormone
- UC: ulcerative colitis
- URI: upper respiratory tract infection
- UV: ultraviolet
- UVA: ultraviolet wavelength A
- UVB: ultraviolet wavelength B
- JVC: ultraviolet wavelength C
- VDRL: venereal disease research laboratory
- VZV: varicella zoster virus
Skin Function

- **protection**
  - due to continuous recycling and avascularity of epidermis
  - barrier to UV radiation, mechanical/chemical insults, pathogens, and dehydration
- **thermal regulation**
  - insulation to maintain body temperature in cool environments via peripheral vasoconstriction, hair, and subcutaneous adipose tissue
  - dissipation of heat in warm environments via increased activity of sweat glands and increased blood flow within dermal vascular networks
- **sensation**
  - touch, pain, and temperature sensation
- **metabolic function**
  - vitamin D synthesis
  - energy storage (mainly in the form of triglycerides)

Definitions

Primary Morphological Lesions

**Definition**
- an initial lesion that has not been altered by trauma or manipulation and has not regressed

<table>
<thead>
<tr>
<th>Profile</th>
<th>&lt;1 cm Diameter</th>
<th>≥1 cm Diameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flat lesion</td>
<td>Macule (e.g. freckle)</td>
<td>Patch (e.g. vitiligo)</td>
</tr>
<tr>
<td>Raised superficial lesion</td>
<td>Papule (e.g. wart)</td>
<td>Plaque (e.g. psoriasis)</td>
</tr>
<tr>
<td>Deep palpable (dermal or subcutaneous)</td>
<td>Nodule (e.g. dermatofibroma)</td>
<td>Tumour (e.g. lipoma)</td>
</tr>
<tr>
<td>Elevated fluid-filled lesions</td>
<td>Vesicle (e.g. HSV)</td>
<td>Bulla (e.g. bullous pemphigoid)</td>
</tr>
</tbody>
</table>

Secondary Morphological Lesions

**Definition**
- develop during the evolutionary process of skin disease, or created by manipulation, or due to complication of primary lesion (e.g. rubbing, scratching, infection)
- **crust**: dried fluid (serum, blood, or purulent exudate) originating from a lesion (e.g. impetigo)
- **scale**: excess keratin (e.g. seborrheic dermatitis)
- **lichenification**: thickening of the skin and accentuation of normal skin markings (e.g. chronic atopic dermatitis)
- **fissure**: a linear slit-like cleavage of the skin
- **excoriation**: a scratch mark
- **erosion**: a disruption of the skin involving the epidermis alone; heals without scarring
- **ulcer**: a disruption of the skin that extends into the dermis or deeper; heals with scarring
- **xerosis**: pathologic dryness of skin (xeroderma), conjunctiva (xerophthalmia), or mucous membranes
- **atrophy**: histological decrease in size and number of cells or tissues, resulting in thinning or depression of the skin
Other Morphological Lesions

- **cyst**: an epithelial-lined collection containing semi-solid or fluid material
- **pustule**: an elevated lesion containing purulent fluid (white, grey, yellow, green)
- **scar**: replacement fibrosis of dermis and subcutaneous tissue (hypertrophic or atrophic)
- **wheal**: a special form of papule or plaque that is transient (<24 h) and blanchable often with a halo and central clearing, formed by edema in the dermis (e.g. urticaria)
- **comedones**: collection of sebum and keratin
  - open comedo (blackhead)
  - closed comedo (not a pustule; rather a minute dome shaped skin coloured papule)
- **petechiae**: small pinpoint extravasation of blood into dermis resulting in hemorrhagic lesions; non-blanchable, <3 mm in size
- **purpura**: larger than petechia, 3 mm-1 cm in size
- **ecchymoses**: larger than purpura, >1 cm in size (i.e. a “bruise”)
- **telangiectasia**: dilated superficial blood vessels; often branching and reticulated and of small caliber

Patterns and Distribution

- **acral**: relating to the hands and feet (e.g. perniosis, secondary syphilis)
- **annular**: ring-shaped (e.g. granuloma annulare)
- **follicular**: involving hair follicles (e.g. folliculitis)
- **guttate**: lesions following a “drop-like” pattern (e.g. guttate psoriasis)
- **Koebner phenomenon**: i.e. isomorphic response, appearance of lesions at an injury site (e.g. lichen planus, psoriasis, vitiligo)
- **morbilliform**: literally meaning “measles-like”, an eruption composed of macules and papules with truncal predominance
- **reticular**: lesions following a net-like pattern (e.g. livedo reticularis)
- **satellite**: small lesions scattered around the periphery of a larger lesion (e.g. candida diaper dermatitis)
- **serpiginous**: lesions following a snake-like pattern (e.g. cutaneous larva migrans)
- **target/targetoid**: concentric ring lesions, like a dartboard (e.g. erythema multiforme)
- **other descriptive terms**: discrete, clustered, linear, confluent, dermatitic, indurated (i.e. hard or firm)
Differential Diagnoses of Common Presentations

Table 3. Cysts

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Clinical Course</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidermal Cyst</td>
<td>Round, yellow/flesh-coloured, slow growing, mobile, firm, fluctuant, nodule or tumour</td>
<td>Epithelial cells displaced into dermis, epidermal lining becomes filled with keratin and lipid-rich debris May be post-traumatic, rarely syndromic</td>
<td>Most common cutaneous cyst in youth – mid age</td>
<td>Central punctum may rupture (foul, cheesy odour, creamy colour) and produce inflammatory reaction Increase in size and number over time, especially in pregnancy Excise completely before it becomes infected</td>
</tr>
<tr>
<td>Pilary Cyst (Trichilemmal)</td>
<td>Multiple, hard, variable sized nodules under the scalp, lacks central punctum</td>
<td>Thick-walled cyst lined with stratified squamous epithelium and filled with dense keratin Idiopathic Post-trauma, often familial</td>
<td>2nd most common cutaneous cyst F&gt;M</td>
<td>Rupture causes pain and inflammation Excision</td>
</tr>
<tr>
<td>Dermoid Cyst</td>
<td>Firm nodule most commonly found at lateral third of eyebrow or midline under nose</td>
<td>Rare, congenital hamartomas, which arise from inclusion of epidermis along embryonal cleft closure lines, creating a thick-walled cyst filled with dense keratin</td>
<td>Rare</td>
<td>If nasal midline, risk of extension into CNS Excision</td>
</tr>
<tr>
<td>Ganglion Cyst</td>
<td>Usually solitary, rubbery, translucent; a clear gelatinous viscous fluid may be extruded</td>
<td>Cystic lesion that originates from joint or tendon sheath, called a digital mucous cyst when found on fingertip Associated with osteoarthrits</td>
<td>Older age</td>
<td>Stable Incision and expression of contents Laser ablation and electrodessication</td>
</tr>
<tr>
<td>Milium</td>
<td>1-2 mm superficial, white to yellow subepidermal papules occurring on eyelids, cheeks, and forehead</td>
<td>Small epidemoid cyst, primarily arising from pluripotential cells in epidermal or adnexal epithelium Can be secondary to blistering, ulceration, trauma, topical corticosteroid atrophy, or cosmetic procedures</td>
<td>Any age 40-50% of infants</td>
<td>In newborns, spontaneously resolves in first 4 wk of life Incision and expression of contents Laser ablation and electrodessication Multiple facialis milia respond to topical retinoid therapy</td>
</tr>
</tbody>
</table>
Fibrous Lesions

dermatofibroma

Clinical Presentation
- button-like, firm dermal papule or nodule, skin-coloured to red-brown colouring
- majority are asymptomatic but may be pruritic and/or tender
- site: legs > arms > trunk
- dimple sign (Fitzpatrick's sign): lateral compression causes dimpling of the lesion

Pathophysiology
- benign tumour due to fibroblast proliferation in the dermis

Etiology
- unknown; may be associated with history of minor trauma (e.g. shaving or insect bites)
- eruptive dermatofibromata can be associated with SLE

Epidemiology
- adults, F>M

Differential Diagnosis
- dermatofibrosarcoma protruberans, MM, Kaposi's sarcoma, blue nevus

Investigations
- biopsy if diagnosis is uncertain

Management
- no treatment required
- excision or cryosurgery if bothersome

Skin Tags

Clinical Presentation
- small (1-10 mm), soft, skin-coloured or darker pedunculated papule, often polypoid
- sites: eyelids, neck, axillae, inframammary, and groin

Pathophysiology
- benign outgrowth of skin

Epidemiology
- middle-aged and elderly, F>M, obese, can increase in size and number during pregnancy

Differential Diagnosis
- pedunculated seborrhoeic keratosis, compound or dermal melanocytic nevus, neurofibroma, fibroepithelioma of Pinkus (rare variant of BCC)

Management
- excision, electrodessication, cryosurgery

Hyperkeratotic Lesions

Seborrhoeic Keratosis

Clinical Presentation
- well-demarcated waxy papule/plaque with classic "stuck on" appearance
- rarely pruritic
- over time lesions appear more warty, greasy and pigmented
- sites: face, trunk, upper extremities (may occur at any site except palms or soles)

Pathophysiology
- very common benign epithelial tumour due to proliferation of keratinocytes and melanocytes

Epidemiology
- unusual <30 yr old
- M>F
- autosomal dominant inheritance

Differential Diagnosis
- MM (lentigo maligna, nodular melanoma), melanocytic nevi, pigmented BCC, solar lentigo, spreading pigmented AK
Investigations
• biopsy only if diagnosis uncertain

Management
• none required, for cosmetics only
• cryotherapy, curettage

ACTINIC KERATOSIS (SOLAR KERATOSIS)
• see Pre-Malignant Skin Conditions, D31

KERATOACANTHOMA
• see Malignant Skin Tumours, D32

Corns

Clinical Presentation
• firm papule with a central, translucent, cone-shaped, hard keratin core
• painful with direct pressure
• sites: most commonly on dorsolateral fifth toe and dorsal aspects of other toes

Pathophysiology
• localized hyperkeratosis induced by pressure on hands and feet

Epidemiology
• F>M, can be caused by chronic microtrauma

Differential Diagnosis
• tinea pedis, plantar warts

Management
• relieve pressure with padding or alternate footwear, orthotics
• paring, curettage

Keloids

Clinical Presentation
• firm, shiny, skin-coloured or red-bluish papules/nodules that most often arise from cutaneous injury (e.g. piercing, surgical scar, acne), but may appear spontaneously
• extends beyond the margins of the original injury, and may continue to expand in size for years with claw-like extensions
• can be pruritic and painful
• sites: earlobes, shoulders, sternum, scapular area

Pathophysiology
• excessive deposition of randomly organized collagen fibres following trauma to skin

Epidemiology
• most common in black patients, followed by those of Asian descent (predilection for darker skin)
• M=F, all age groups

Management
• intralesional corticosteroid injections
• cryotherapy
• silicone compression

Corns vs. Warts vs. Calluses
• Corns have a whitish yellow central translucent keratinous core; painful with direct pressure
• Warts bleed with paring and have a black speckled central appearance due to thrombosed capillaries; plantar warts destroy dermatoglyphics (epidermal ridges)
• Calluses have layers of yellowish keratin revealed with paring; there are no thrombosed capillaries or interruption of epidermal ridges

Keloids vs. Hypertrophic Scars
• Keloids: extend beyond margins of original injury with claw-like extensions
• Hypertrophic scars: confined to original margins of injury
**Pigmented Lesions**

**CONGENITAL NEVOMELANOCYTIC NEVI (CNMN)**

**Clinical Presentation**
- sharply demarcated pigmented papule or plaque with regular borders ± coarse hairs
- classified by size: small (<1.5 cm), medium (M1: 1.5-10 cm, M2: >10-20 cm), large (L1: >20-30 cm, L2 >30-40 cm), giant (G1: >40-60 cm, G2: >60 cm)
- may be surrounded by smaller satellite nevi

**Pathophysiology**
- nevomelanocytes in epidermis (clusters) and dermis (strands)

**Epidemiology**
- present at birth or develops in early infancy to childhood
- malignant transformation is rare (1-5%) and more correlated with size of the lesion
- neurocutaneous melanosis can occur in giant CNMN (melanocytes in the central nervous system)

**Management**
- surgical excision if suspicious, due to increased risk of melanoma
- MRI if suspicious for neurological involvement

**OTHER CONGENITAL PIGMENTED LESIONS**

<table>
<thead>
<tr>
<th>Table 4. Comparison of Other Congenital Pigmented Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Presentation</strong></td>
</tr>
<tr>
<td>----------------------------</td>
</tr>
<tr>
<td>Café-au-lait macule</td>
</tr>
<tr>
<td>Speckled lentiginous nevus (nevus spilus)</td>
</tr>
<tr>
<td>Dermal Melanocytosis (historically known as Mongolian Spot)</td>
</tr>
</tbody>
</table>

**ACQUIRED NEVOMELANOCYTIC NEVI**

**Clinical Presentation**
- common mole: well circumscribed, round, uniformly pigmented macules/papules <1.5 cm
- average number of moles per person: 18-40
- 3 stages of evolution: junctional NMN, compound NMN, and dermal NMN

**Table 5. Evolution of Acquired Nevomelanocytic Nevii**

<table>
<thead>
<tr>
<th>Type</th>
<th>Age of Onset</th>
<th>Clinical Presentation</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Junctional</td>
<td>Childhood Majority progress to compound nevus</td>
<td>Flat, irregularly bordered, uniformly tan-dark brown, sharply demarcated smooth macule</td>
<td>Melanocytes at dermal-epidermal junction above basement membrane</td>
</tr>
<tr>
<td>Compound</td>
<td>Any age</td>
<td>Dome, regularly bordered, smooth, round, tan-dark brown papule</td>
<td>Melanocytes at dermal-epidermal junction; migration into dermis</td>
</tr>
<tr>
<td>Dermal</td>
<td>Adults</td>
<td>Soft, dome-shaped, skin-coloured to tan/brown papules or nodules, often with telangiectasia</td>
<td>Melanocytes exclusively in dermis</td>
</tr>
</tbody>
</table>

**DDx of Hyperpigmented Macules**
- Purpura (e.g. solar, ASA, anti-coagulants, steroids, hemosiderin stain)
- Post-inflammatory
- Melasma
- Melanoma
- Fixed drug eruption

**Other Nevii**
- Halo nevus: often a typical appearing nevus surround by a ring of depigmentation; not rare in children; uncommonly associated with vitiligo; no treatment required unless irregular colour or borders
- Blue nevus: round to oval macule/papule with homogenous blue to blue-black colour; often appears in childhood and late adolescence; no treatment required unless atypical features are noted
Management

- new or changing pigmented lesions should be evaluated for atypical features which could be indicative of melanoma
- excisional biopsy can be considered if the lesion demonstrates asymmetry, varied colours, irregular borders, pruritis or persistent bleeding

OTHER ACQUIRED PIGMENTED LESIONS

Table 6. Comparison of Other Acquired Pigmented Lesions

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Differential Diagnosis</th>
<th>Clinical Course and Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atypical nevus (dysplastic nevus)</td>
<td>Variegated macule/papule with irregular distinct melanocytes in the basal layer Risk factors: family history</td>
<td>Hyperplasia and proliferation of melanocytes extending beyond dermal compartment of the nevus Often with region of adjacent nests</td>
<td>&gt;5 atypical nevi increases risk for melanoma Numerous dysplastic nevi may be part of Familial Atypical Mole and Melanoma syndrome</td>
<td>Follow with colour photographs for changes Excisional biopsy if lesion changing or highly atypical</td>
</tr>
<tr>
<td>Ephelides (freckles)</td>
<td>Small (&lt;5 mm) well-demarcated light brown macules Sites: sun-exposed skin</td>
<td>Increased melanin within basal layer keratinocytes secondary to sun exposure</td>
<td>Skin phototypes I-II</td>
<td>Junctional nevi Juvenile lentigines</td>
</tr>
<tr>
<td>Solar Lentigo (Liver Spot)</td>
<td>Well-demarcated brown/black irregular macules Sites: sun-exposed skin</td>
<td>Benign melanocytic proliferation in dermal-epidermal junction due to chronic sun exposure</td>
<td>Most common in Caucasians &gt;40 yr Skin phototypes I-III</td>
<td>Lentigo maligna, seborrhoeic keratosis, pigmented solar keratosis</td>
</tr>
<tr>
<td>Becker’s Nevus</td>
<td>Hairy, light brown macule/patch with a papular verrucous surface Sites: trunk and shoulders, onset in teen years</td>
<td>Pigmented hamartoma with increased melanin in basal cells</td>
<td>M:F Often becomes noticeable at puberty</td>
<td>Hairy congenital melanocytic nevus</td>
</tr>
<tr>
<td>Melasma</td>
<td>Dark, usually symmetrical, skin discolouration on sun-exposed areas of face (forehead, upper lip, cheeks, chin)</td>
<td>Increase in number and activity of melanocytes Associated with estrogen and progesterone</td>
<td>F&gt;M Common in pregnancy and women taking OCP or HRT Risk factors: sun exposure, dark skin tone Can occur with mild endocrine disturbances, antiepileptic medications and other photosensitizing drugs</td>
<td>Post-inflammatory hyperpigmentation, Riehl melanosis</td>
</tr>
</tbody>
</table>

Vascular Lesions

Table 7. Vascular Tumours Compared to Vascular Malformations

<table>
<thead>
<tr>
<th>Vascular Tumours</th>
<th>Vascular Malformations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Endothelial hyperplasia Congenital malformation with normal endothelial turnover</td>
</tr>
<tr>
<td>Presence at Birth</td>
<td>Usually postnatal 100% at birth (not always obvious)</td>
</tr>
<tr>
<td>M:F</td>
<td>1:3-5 1:1</td>
</tr>
<tr>
<td>Natural History</td>
<td>Phases • Proliferating • Involuting • Involved Proportionate growth (can expand)</td>
</tr>
</tbody>
</table>

HEMANGIOMAS

Clinical Presentation

- red or blue subcutaneous mass that is soft/compressible, blanches with pressure; feels like a “bag of worms” when palpated

Pathophysiology

- benign vascular tumour
- includes: cavernous hemangioma, capillary/infantile hemangioma, spider hemangioma

A spider angioma will blanch when the tip of a paperclip is applied to the centre of the lesion.
### Table 8. Vascular Tumours

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Epidemiology</th>
<th>Clinical Course</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemangioma of infancy</td>
<td>Hot, firm red to blue plaques or tumours</td>
<td>Benign vascular proliferation of endothelial lining</td>
<td>Appears shortly after birth; rarely may be congenital</td>
<td>Appears shortly after birth, increases in size over months, then regresses 50% of lesions resolve spontaneously by 5 yr</td>
<td>10% require treatment due to functional impairment (visual compromise, airway obstruction, high output cardiac failure) or cosmesis Consider treatment if not gone by school age; propranolol; systemic corticosteroids; laser treatment; surgery</td>
</tr>
<tr>
<td>Spider Angioma (Campbell Telangiectasia)</td>
<td>Central red arteriole with slender branches, faintly pulsatile, blanchable</td>
<td>Can be associated with hyperesthetic state (e.g. in hepatocellular disease, pregnancy, OCP) but often is not</td>
<td>Increase in number over time</td>
<td>Reassurance</td>
<td>Electrodesiccation or laser surgery if patient wishes</td>
</tr>
<tr>
<td>Cherry Angioma (Campbell De Morgan Spot)</td>
<td>Bright red to deep maroon, dome-shaped vascular papules, 1-5 mm</td>
<td>Benign vascular neoplasm</td>
<td>&gt; 30 yr old</td>
<td>Lesions do not fade in time</td>
<td>Usually no treatment needed Laser or electrocautery for small lesions Excision of large lesions if necessary</td>
</tr>
<tr>
<td>Pyogenic Granuloma</td>
<td>Bright red, dome-shaped sessile or pedunculated friable nodule</td>
<td>Rapidly developing hemangioma Proflation of capillaries with erosion of epidermis and neutrophilia</td>
<td>&lt;30 yr old</td>
<td>Lesions bleed infrequently</td>
<td>Surgical excision with histologic examination Electrocautery; laser; cryotherapy</td>
</tr>
</tbody>
</table>

### Vascular Malformations

### Table 9. Vascular Malformations

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Presentation</th>
<th>Pathophysiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevus Flammeus (Port-wine stain)</td>
<td>Red to blue macule present at birth that follows a dermatomal distribution, rarely crosses midline</td>
<td>Congenital vascular malformation of dermal capillaries; rarely associated with Sturge-Weber syndrome (V1, V2 distribution)</td>
<td>Laser or make-up</td>
</tr>
<tr>
<td>Nevus Simplex (salmon patch)</td>
<td>Pink-red irregular patches</td>
<td>Congenital dilation of dermal capillaries</td>
<td>No treatment required</td>
</tr>
</tbody>
</table>

### Lipoma

**Clinical Presentation**
- single or multiple non-tender subcutaneous tumours that are soft and mobile
- occurs most frequently on the trunk, and extremities but can be anywhere on the body

**Pathophysiology**
- adipocytes enclosed in a fibrous capsule

**Epidemiology**
- often solitary or few in number, if multiple can be associated with rare syndromes

**Differential Diagnosis**
- angiolipoma, liposarcoma

**Investigations**
- biopsy only if atypical features (painful, rapid growth, firm)

**Management**
- reassurance
- excision or liposuction only if desired for cosmetic purposes
Acneform Eruptions

Acne Vulgaris/Common Acne

Clinical Presentation
• A common inflammatory pilosebaceous disease categorized with respect to severity
  ▪ Type I: comedonal, sparse, no scarring
  ▪ Type II: comedonal, papular, moderate ± little scarring
  ▪ Type III: comedonal, papular, and pustular, with scarring
  ▪ Type IV: nodulocystic acne, risk of severe scarring
• Sites of predilection: face, neck, upper chest, and back

Pathophysiology
• Hyperkeratinization at the follicular ostia (opening) blocks the secretion of sebum leading to the formation of microcomedones
• Androgens promote excess sebum production
• Propionibacterium acnes metabolize sebum to free fatty acids and produces pro-inflammatory mediators

Epidemiology
• Age of onset in puberty (10-17 yr in females, 14-19 yr in males)
• In prepubertal children consider underlying hormonal abnormality (e.g. late onset congenital adrenal hyperplasia)
• More severe in males than in females
• Incidence decreases in adulthood
• Genetic predisposition: majority of individuals with cystic acne have parent(s) with history of severe acne

Differential Diagnosis
• Folliculitis, keratosis pilaris (upper arms, face, thighs), perioral dermatitis, rosacea

Table 10. Management of Acne

<table>
<thead>
<tr>
<th>Compound/Drug Class</th>
<th>Product Names</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>MILD ACNE: Topical Therapies OTC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoyl peroxide (BPO)</td>
<td>Solugel, Benzac, Desquam, Fostex</td>
<td>Helps prevent P. acnes resistance, is a bactericidal agent (targets P. acnes) and is comedolytic</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>Akurza® Cream, DermalZone</td>
<td>Used when patients cannot tolerate a topical retinoid due to skin irritation</td>
</tr>
<tr>
<td>MILD ACNE: Prescription Topical Therapies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Clindamycin (Dalacin T), Erythromycin</td>
<td>High rate of resistance when used as monotherapy</td>
</tr>
<tr>
<td>Retinoids</td>
<td>Vitamin A Acid (Tretinoin, Stieva-A, Retin A) Adapalene (Differin)</td>
<td>Backbone of topical acne therapy. All regimens should include a retinoid unless patient cannot tolerate</td>
</tr>
<tr>
<td>Combination products</td>
<td>Clindoxyl (Clindamycin and BPO) Benzacin (Clindamycin and BPO) Tactuo (Adapalene and BPO) Stevamycin (Tretinoin and Erythromycin) Benzamycine (BPO and Erythromycin)</td>
<td>Allows for greater adherence and efficacy. Combines different mechanisms of action to increase efficacy and maximize tolerability</td>
</tr>
<tr>
<td>MODERATE ACNE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetracycline/Minocycline/ Doxycycline</td>
<td>Sumycin/Minocin/Vibramycin</td>
<td>Use caution with regard to drug interactions: do not use with isotretinoin. Sun sensitivity. Antibiotics require 3 mo of use before assessing efficacy</td>
</tr>
<tr>
<td>Cyproterone acetate-ethinyl estradiol</td>
<td>Diane-35®</td>
<td>After 35 yr of age, estrogen/progesterone should only be considered in exceptional circumstances, carefully weighing the risk/benefit ratio with physician guidance</td>
</tr>
<tr>
<td>Spironolactone (source ADA)</td>
<td>Aldactone</td>
<td>May cause hyperkalemia at higher doses. Black box warning for breast cancer</td>
</tr>
</tbody>
</table>

Acne Myths Debunked
• Eating greasy food and chocolate does not cause or worsen acne
• Blackheads (comedones) are black because of oxidized fatty acids, not dirt
• Acne is not caused by poor hygiene; on the contrary, excessive washing of face can be an aggravator

Acne Exacerbating Factors
• Systemic medications: lithium, phenytoin, steroids, halogens, androgens, iodides, bromides, danazol
• Topical agents: steroids, tars, ointments, oily cosmetics
• Mechanical pressure or occlusion, such as leaning face on hands
• Emotional stress

Antibiotics are used in inflammatory skin conditions since they also have anti-inflammatory properties (e.g. macrolides in acne). Topical antibiotics may also be used to treat secondary bacterial superinfections (e.g. impetigo)

Intralesional Injections
Intralesional corticosteroid injections are effective in the treatment of individual acne nodules

Treatment of Acne Scars
• Tretinoin creams
• Microdermabrasion for superficial scars
• Injectable fillers (collagen, hyaluronic acid)
• Fraxel laser

A combination of topical retinoids and topical erythromycin or clindamycin is more effective than either agent used alone
**Perioral Dermatitis**

**Clinical Presentation**
- discrete erythematous micropapules that often become confluent, forming inflammatory plaques on perioral, perinasal, and periorbital skin
- commonly symmetrical, rim of sparing around vermillion border of lips

**Epidemiology**
- 15-40 yr old, occasionally in younger children
- predominantly females

**Differential Diagnosis**
- contact dermatitis, rosacea, acne vulgaris

**Management**
- avoid all topical steroids
- topical: metronidazole 0.75% gel or 0.75-1% cream to affected area bid
- systemic: tetracycline family antibiotic (utilized for its anti-inflammatory properties)

---

**Rosacea**

**Clinical Presentation**
- dome-shaped inflammatory papules ± pustules
- flushing, non-transient erythema, and telangiectasia
- distribution: typically on central face including forehead, nose, cheeks, and chin; rarely on scalp, neck, and upper body
- characterized by remissions and exacerbations
- exacerbating factors: heat, cold, wind, sun, stress, drinking hot liquids, alcohol, caffeine, spices
- all forms of rosacea can progress from mild to moderate to severe
- rarely in longstanding rosacea, signs of thickening, induration and lymphedema in the skin can develop
  - phyma: a distinct swelling caused by lymphedema and hypertrophy of subcutaneous tissue, particularly affecting the nose (rhinophyma)
  - ocular manifestations: blepharoconjunctivitis, keratitis, iritis

**Pathophysiology**
- unknown

**Epidemiology**
- although found in all skin types, highest prevalence in fair-skinned people
- 30-50 yr old; F>M

**Differential Diagnosis**
- acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis

**Management**
- trigger avoidance is key to long-term management
- avoid topical corticosteroids
- telangiectasia: treated by physical ablation; electrical hyfrecators, vascular lasers, and intense pulsed light therapies
- phymas: treated by physical ablation or removal; paring, electrosurgery, cryotherapy, laser therapy (CO2, argon, Nd:YAG)
### Table 11. Specific Rosacea Treatments

<table>
<thead>
<tr>
<th>1st Line</th>
<th>2nd Line</th>
<th>3rd Line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral tetracyclines (250-500 mg PO bid)</td>
<td>Topical clindamycin</td>
<td>Oral retinoids</td>
</tr>
<tr>
<td>Topical metronidazole</td>
<td>Topical erythromycin 2% solution</td>
<td>Topical sulfur</td>
</tr>
<tr>
<td>Oral erythromycin (250-500 mg PO bid)</td>
<td>Topical benzoyl peroxide</td>
<td></td>
</tr>
<tr>
<td>Topical azelaic acid</td>
<td>Oral metronidazole</td>
<td></td>
</tr>
<tr>
<td>Topical clindamycin</td>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td>Topical erythromycin 2% solution</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topical benzoyl peroxide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral metronidazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Dermatitis (Eczema)

**Definition**
- inflammation of the skin

**Clinical Presentation**
- poorly demarcated erythematous patches or plaques
- symptoms include pruritus and pain
- acute dermatitis: papules, vesicles
- subacute dermatitis: scaling, crusting
- chronic dermatitis: lichenification, xerosis, fissuring

### Asteatotic Dermatitis

**Clinical Presentation**
- diffuse, mild pruritic dermatitis secondary to dry skin
- very common in elderly, especially in the winter (i.e. “winter itch”) but starts in the fall
- shins predominate, looks like a “dried river bed”

**Management**
- skin rehydration with moisturizing routine ± mild corticosteroid creams

### Atopic Dermatitis

**Clinical Presentation**
- subacute and chronic eczematous reaction associated with prolonged severe pruritus
- distribution depends on age
- inflammation, lichenification, excoriation are secondary to relentless scratching
- atopic palms: hyperlinearity of the palms (associated with ichthyosis vulgaris)
- associated with: keratosis pilaris (hyperkeratosis of hair follicles, “chicken skin”), xerosis, occupational hand dryness

**Epidemiology**
- frequently affects infants, children, and young adults
- almost 15% of children in developed countries under the age of 5 are affected
- associated with personal or family history of atopy (asthma, hay fever, anaphylaxis, eosinophilia)
- polygenic inheritance: one parent >60% chance for child; two parents >80% chance for child
- the earlier the onset, the more severe and persistent the disease
- long-term condition with 1/3 of patients continuing to show signs of AD into adulthood

**Pathophysiology**
- a T-cell driven process with epidermal barrier dysfunction

**Investigations**
- clinical diagnosis
- consider: skin biopsy, immunoglobulin serum levels (often elevated serum IgE level), patch testing, and skin prick tests

**Management**
- goal: reduce signs and symptoms, prevent or reduce recurrences/flares
- better outcome (e.g. less flare-ups, modified course of disease) if diagnosis made early and treatment plan individualized
- avoid triggers of AD
- non-pharmacologic therapy
  - moisturizers
    - apply liberally and reapply frequently with goal of minimizing xerosis
    - include in treatment of mild to severe disease as well as in maintenance therapy

### Triggers for Atopic Dermatitis
- Irritants (detergents, solvents, clothing, water hardness)
- Contact allergens
- Environmental aeroallergens (e.g. dust mites)
- Inappropriate bathing habits (e.g. long hot showers)
- Sweating
- Microbes (e.g. S. aureus)
- Stress

![Figure 4. Atopic dermatitis distribution](image)
bathing practices
- bathe in plain warm water for a short period of time once daily followed by lightly but not completely drying the skin with a towel; immediate application of topical agents or moisturizers after this
- use fragrance-free hypoallergenic non-soap cleansers

pharmacologic therapy
- topical corticosteroids
  - effective in reducing acute and chronic symptoms as well as prevention of flares
  - choice of steroid potency depends on age, body site, short vs. long-term use
  - apply 1 adult fingertip unit (0.5 g) to an area the size of 2 adult palms 2x/d for acute flares, and 1-2x/wk for maintenance therapy
  - local side effects: skin atrophy, purpura, telangiectasia, striae, hypertrichosis, and acneform eruption are all very rarely seen
- topical calcineurin inhibitors
  - tacrolimus 0.03%, 0.1% (Protopic®) and pimecrolimus 1% (Elidel®)
  - use as steroid-sparing agents in the long-term
  - advantages over long-term corticosteroid use: rapid, sustained effect in controlling pruritus; safe for the face and neck
  - apply 2x/d for acute flares, and 2-3x/wk to recurrent sites to prevent relapses
  - local side effects: stinging, burning, allergic contact dermatitis
  - U.S. black box warning of malignancy risk: rare cases of skin cancer and lymphoma reported; no causal relationship established

Complications
- infections
  - topical mupirocin or fusidic acid (Canada only, not available in US)
  - oral antibiotics (e.g. cloxacillin, cephalaxin) for widespread S. aureus infections

Initial assessment of disease history, extent, and severity (impact on family, psychological distress)
- Patient education, daily emollient use

Adjunctive therapy
- Avoidance of triggers
- Treat bacterial superinfections (topical or oral antibiotics)
- Antihistamines
- Psychological interventions

Acute control of flare
- Topical corticosteroids or topical calcineurin inhibitor (pimecrolimus or tacrolimus)

Disease remission (no signs or symptoms)
- Use of topical corticosteroid or calcineurin inhibitor at earliest sign of flare
- Long-term maintenance use of calcineurin inhibitors

Maintenance therapy if disease is persistent and/or frequent recurrences
- Use of topical corticosteroid or calcineurin inhibitor at earliest sign of flare
- Long-term maintenance use of calcineurin inhibitors

Severe refractory disease
- Azathioprine
- Methotrexate
- Oral cyclosporin
- Oral steroids
- Phototherapy
- Potent topical steroids
- Psychotherapeutics

Figure 5. Atopic dermatitis treatment algorithm
Contact Dermatitis

Clinical Presentation
• cutaneous inflammation caused by an external agent(s)

Table 12. Contact Dermatitis

<table>
<thead>
<tr>
<th>Mechanism of Reaction</th>
<th>Irritant Contact Dermatitis</th>
<th>Allergic Contact Dermatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: quick reaction, sharp margins (e.g. from acid/alkali exposure)</td>
<td>Toxic injury to skin; non-immune mechanism</td>
<td>Cell-mediated delayed (Type IV) hypersensitivity reaction (see Rheumatology, RH2)</td>
</tr>
<tr>
<td>Cumulative insult: slow to appear, poorly defined margins (e.g. from soap), more common</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Type of Reaction | Erythema, dryness, fine scale, burning | Erythema with a papulovesicular eruption, swelling, pruritus |

| Frequency | Majority; will occur in anyone given sufficient concentration of irritants | Minority; patient acquires susceptibility to allergen that persists indefinitely |
| Distribution | Hands are the most common site | Areas exposed to allergen |
| Examples | Soaps, weak alkali, detergents, organic solvents, alcohol, oils | Many allergens are irritants, so may coincide with irritant dermatitis |
| Management | Avoidance of irritants, Wet compresses with Burow’s solution, Barrier moisturizers, Topical/oral steroids | Patch testing to determine specific allergen, Avoid allergen and its cross-reactants, Wet compresses soaked in Burow’s solution (drying agent), Steroid cream (e.g. hydrocortisone 1%, betamethasone valerate 0.05% or 0.1% cream; bid), Systemic steroids prn (prednisone 1 mg/kg, taper over 2 wk) |

Dyshidrotic Dermatitis

Clinical Presentation
• “tapioca pudding” papulovesicular dermatitis of hands and feet that coalesce into plaques, followed by painful fissuring
• acute stage often very pruritic
• secondary infection common
• lesions heal with desquamation and may lead to chronic lichenification
• sites: palms and soles ± dorsal surfaces of hands and feet

Pathophysiology
• NOT caused by hyperhidrosis (excessive sweating)
• emotional stress may precipitate flares

Management
• topical: high potency corticosteroid with plastic cling wrap occlusion to increase penetration
• intralesional triamcinolone injection
• systemic:
  ▪ prednisone in severe cases
  ▪ antibiotics for secondary S. aureus infection

Nummular Dermatitis

Clinical Presentation
• annular, coin-shaped, pruritic, dry, scaly, erythematous plaques, can become lichenified
• often associated with atopic and dyshidrotic dermatitis
• secondary infection common

Pathophysiology
• little is known, but it is often accompanied by xerosis, which results from a dysfunction of the epidermal lipid barrier; this in turn can allow permeation of environmental agents, which can induce an allergic or irritant response

Management
• moisturization
• mid to high potency corticosteroid ointment bid
**Seborrheic Dermatitis**

**Clinical Presentation**
- greasy, erythematous, yellow, scaling, minimally elevated papules and plaques in areas rich in sebaceous glands, can look moist and superficially eroded in flexural regions
- infants: “cradle cap”
- children: may be generalized with flexural and scalp involvement
- adults: diffuse involvement of scalp margin with yellow to white flakes, pruritus, and underlying erythema
- sites: scalp, eyebrows, eyelashes, beard, glabella, post-auricular, over sternum, trunk, body folds, genitalia

**Pathophysiology**
- possible etiologic association with *Malassezia* spp. (yeast)

**Epidemiology**
- common in infants and adolescents
- increased incidence and severity in immunocompromised patients
- in adults, can cause dandruff (pityriasis sicca)

**Management**
- face: ketoconazole (Nizoral®) cream daily or bid + mild steroid cream daily or bid
- scalp: salicylic acid in olive oil or Derma-Smoothe FS® lotion (peanut oil, mineral oil, fluocinolone acetonide 0.01%) to remove dense scales, 2% ketoconazole shampoo (Nizoral®), ciclopirox (Stieprox®) shampoo, selenium sulfide (e.g. Selsun®) or zinc pyrithione (e.g. Head and Shoulders®) shampoo, steroid lotion (e.g. betamethasone valerate 0.1% lotion bid)

**Stasis Dermatitis**

**Clinical Presentation**
- erythematous, scaly, pruritic plaques in lower legs, particularly the medial ankle
- brown hemosiderin deposition, woody fibrosis, atrophy blanche, and lipodermatosclerosis in late stages

**Pathophysiology**
- chronic venous insufficiency leads to venous stasis
- surrounding soft tissue inflammation and fibrosis results

**Investigations**
- Doppler and colour-coded Duplex sonography if suspicious for DVT
- culture for MRSA if there is crusting

**Management**
- compression stockings
- rest and elevate legs (above the level of the heart)
- moisturizer to treat xerosis
- mid-high potency topical corticosteroids to control inflammation

**Complications**
- ulceration (common at medial malleolus), secondary bacterial infections

**Lichen Simplex Chronicus**

**Clinical Presentation**
- well-defined plaque(s) of lichenified skin with decreased skin markings + excoriations
- common sites: neck, scalp, lower extremeties, urogenital area
- often seen in patients with atopy

**Pathophysiology**
- skin hyperexcitable to itch, continued rubbing/scratching of skin results
- eventually lichenification occurs

**Investigations**
- if patient has generalized pruritus, rule out systemic cause: CBC with differential count, transaminases, renal and thyroid function tests
- CXR if lymphoma suspected

**Management**
- antipruritics (e.g. antihistamines, topical or intralesional glucocorticoids, Unna boot)
Lichen Planus

Clinical Presentation
- acute or chronic inflammation of mucous membranes or skin, especially on flexural surfaces
- morphology: pruritic, well-demarcated, violaceous, polygonal, flat-topped papules
- common sites: wrists, ankles, mucous membranes in 60% (mouth, vulva, glans), nails, scalp
- distribution: symmetrical and bilateral
- Wickham's striae: reticulate white-grey lines over surface; pathognomonic but may not be present
- mucous membrane lesions: lacy, whitish reticular network, milky-white plaques/papules; increased risk of SCC in erosions and ulcers
- nails: longitudinal ridging; dystrophic; pterygium formation
- scalp: scarring alopecia with perifollicular hyperkeratosis
- spontaneously resolves but may last for weeks, months or years (mouth and skin lesions)
- rarely associated with hepatitis C
- Koebner phenomenon

Pathophysiology
- autoimmune, antigen unknown
- lymphocyte activation leads to keratinocyte apoptosis

Epidemiology
- 1%
- 30-60 yr old, F>M

Investigations
- biopsy
- hepatitis C serology if patient has risk factors

Management
- topical or intralesional corticosteroids
- short courses of oral prednisone (rarely)
- phototherapy for generalized or resistant cases
- oral retinoids for erosive lichen planus in mouth
- systemic immunosuppressants (e.g. azathioprine, methotrexate, cyclosporine)

The 6 Ps of Lichen Planus
- Purple
- Pruritic
- Polygonal
- Peripheral
- Papules
- Penis (i.e. mucosa)

Pityriasis Rosea

Clinical Presentation
- acute, self-limiting eruption characterized by red, oval plaques/patches with central scale that does not extend to edge of lesion
- long axis of lesions follows skin tension lines (i.e. Langer's Lines) parallel to ribs producing “Christmas tree” pattern on back
- varied degree of pruritus
- most start with a "herald" patch which precedes other lesions by 1-2 wk
- common sites: trunk, proximal aspects of arms and legs

Etiology
- suspected HHV-7 or HHV-6 reactivation

Investigations
- none required

Management
- none required; clears spontaneously in 6-12 wk
- symptomatic: topical glucocorticoids if pruritic
Psoriasis

Classification
1. plaque psoriasis
2. guttate psoriasis
3. erythrodermic psoriasis
4. pustular psoriasis
5. inverse psoriasis

Pathophysiology
- not fully understood, genetic and immunologic factors
- shortened keratinocyte cell cycle leads to Th1- and Th17-mediated inflammatory response

Epidemiology
- 1.5-2%, M>F
- all ages: peaks of onset: 20-30 and 50-60
- polygenic inheritance: 8% with 1 affected parent, 41% with both parents affected
- risk factors: smoking, obesity, alcohol, drugs, infections

Differential Diagnosis
- AD, mycosis fungoides (cutaneous T-cell lymphoma), seborrheic dermatitis, tinea, nummular dermatitis, lichen planus

Investigations
- biopsy (if atypical presentation, rarely needed)

1. PLATEAU PSORIASIS

Clinical Presentation
- chronic and recurrent disease characterized by well-circumscribed erythematous papules/plaques with silvery-white scales
- often worse in winter (lack of sun and humidity)
- Auspitz sign: bleeds from minute points when scale is removed
- common sites: scalp, extensor surfaces of elbows and knees, trunk (especially buttocks), nails, pressure areas

Management
- principles of management depends on severity of disease, as defined by BSA affected or less commonly Psoriasis Area and Severity Index (PASI)
  - mild (<5% BSA)
    - topical steroids, topical vitamin D3 analogues, or a combinations of the two are first line
    - topical retinoid ± topical steroid combination, anthralin, and tar are also effective but tend to have more side effects than first line therapies
    - emollients potentiate the effect of topical therapies
    - phototherapy or systemic treatment may be necessary if the lesions are scattered or if it involves sites that are difficult to treat such as palms, soles, scalp, genitals
  - moderate (5-10% BSA) to severe (>10% BSA)
    - goal of treatment is to attain symptom control that is adequate from patient’s perspective
    - phototherapy if accessible
    - systemic or biological therapy based on patient’s treatment history and comorbidities
    - topical steroid ± topical vitamin D3 analogue as adjunct therapy

Table 13. Topical Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emollients</td>
<td>Reduce fissure formation</td>
<td>Petroleum is effective</td>
</tr>
<tr>
<td>Salicylic acid 1-12%</td>
<td>Remove scales</td>
<td></td>
</tr>
<tr>
<td>Tar (LCD: liquor carbonis detergens)</td>
<td>Inhibits DNA synthesis, increases cell turnover</td>
<td>Poor long-term compliance</td>
</tr>
<tr>
<td>Topical Corticosteroids</td>
<td>Reduce scaling and thickness</td>
<td>Use appropriate potency steroid in different areas for degree of psoriasis</td>
</tr>
<tr>
<td>Vitamin D3 analogues:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcipotriene /calcipotriol</td>
<td>Binds to skin</td>
<td>Can be used on face and skin folds</td>
</tr>
<tr>
<td>(Dovonex®, Slikis®)</td>
<td>1,25-dihydroxyvitamin D3 to inhibit keratinocyte proliferation</td>
<td></td>
</tr>
<tr>
<td>Betamethasone + calcipotriene</td>
<td>Combined corticosteroid and vitamin D3 analogue. See above mechanisms</td>
<td>Not to be used on face and folds</td>
</tr>
<tr>
<td>(Dovobet®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tazarotene (Tazorac®) (gel/cream)</td>
<td>Retinoid derivative, decreased scaling</td>
<td>Use on nails</td>
</tr>
</tbody>
</table>

PSORIASIS: Presentation and Pathophysiology
- Pink papules/Plaques/Point bleeding (Auspitz sign)/Physical injury (Koebner phenomenon)
- Silver scale/Sharp margins
- Nail findings: pitting/onycholysis/Oil spots/subungual hyperkeratosis/red lunula/
- Itching (sometimes)
- Immunologic with Th 1 and Th 17 helper cells being actively involved in the pathogenesis

PSORIASIS: Triggers
- Physical trauma (Koebner phenomenon)
- Infections (acute streptococcal infection precipitates guttate psoriasis)
- Stress (can be a major factor in flares)
- Drugs (rebound from stopping systemic glucocorticoids, lithium, antimalarial drugs, interferon)
- Smoking and heavy alcohol consumption

Mechanism of Biologics
- "-mab" = monoclonal antibody
- "-cept" = receptor

Topical Treatments for Chronic Plaque Psoriasis

Cochrane DB Syr Rev 2009;2:CD005028

Study: Systematic review of randomised trials comparing treatments against placebo or against vitamin D.

Patients: 21,448 patients with chronic plaque psoriasis

Intervention: Corticosteroids, dithranol, tazarotene, salicylic acid, methotrexate, macrolactams, vitamin D, and vitamin D + corticosteroids.


Results: Corticosteroids, vitamin D, dithranol, and tazarotene performed better than placebo alone. A combination of corticosteroids and vitamin D were better than either vitamin D or corticosteroids alone.

Calcipotriol is a Vitamin D Derivative

Dovobet® = calcipotriene combined with betamethasone dipropionate and is considered to be one of the most potent topical psoriatic therapies
Table 14. Systemic Treatment of Psoriasis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Considerations</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin</td>
<td>More effective when used in combination with phototherapy</td>
<td>Alopecia, chelitis, teratogenicity, hepatotoxicity, photosensitivity, epistaxis, xerosis, hypertriglyceridemia</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>Used for intermittent control rather than continuously Avoid using for &gt; 1 yr</td>
<td>Renal toxicity, hypertension, hypertriglyceridemia, immunosuppression, lymphoma</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Has been used for over 50 yr</td>
<td>Bone marrow toxicity, hepatic cirrhosis, teratogenicity</td>
</tr>
<tr>
<td>Apremilast (Otezla®)</td>
<td>Extremely safe</td>
<td>GI upset, headache, weight loss</td>
</tr>
<tr>
<td>PUVA</td>
<td>Highly effective in achieving remission Avoid &gt; 200 sessions in lifetime</td>
<td>Pruritus, burning, cataracts, skin cancer</td>
</tr>
<tr>
<td>UVB and “Narrow band” UVB (311-312 nm)</td>
<td>Much less carcinogenic than PUVA</td>
<td>Rare burning</td>
</tr>
</tbody>
</table>

Table 15. Biologics Approved in Canada

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Route</th>
<th>Dosing Schedule</th>
<th>Effectiveness</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etanercept (Enbrel®)*</td>
<td>SC</td>
<td>50 mg twice weekly for 3 mo, then 50 mg weekly</td>
<td>+++</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>Adalimumab (Humira®)*</td>
<td>SC</td>
<td>80 mg x 1, then 40 mg at wk 1 and every 2 wk thereafter</td>
<td>+++++</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>Infliximab (Remicade®)*</td>
<td>IV</td>
<td>5 mg/kg at wk 0, 2, 6 and every 8 wk thereafter</td>
<td>++++++</td>
<td>Anti-TNF</td>
</tr>
<tr>
<td>Ustekinumab (Stelara®)</td>
<td>SC</td>
<td>45 mg or 90 mg at wk 0, 4 and every 12 wk thereafter</td>
<td>++++</td>
<td>Anti-IL 12/23</td>
</tr>
<tr>
<td>Secukinumab (Cosentyx®)</td>
<td>SC</td>
<td>300 mg at week 0, 1, 2, 3, 4 and every 4 weeks thereafter</td>
<td>++++++</td>
<td>Anti-IL 17A</td>
</tr>
</tbody>
</table>

*Can also be used to treat psoriatic arthritis

- biologics under study for treatment of psoriasis: secukinumab, brodalumab, ixekizumab, tildrakizumab, guselkumab

2. GUTTATE PSORIASIS (“DROP-LIKE”)

Clinical Presentation
- discrete, scattered salmon-pink small scaling papules
- sites: diffuse, usually on trunk and legs, sparing palms and soles
- often antecedent streptococcal pharyngitis

Management
- UVB phototherapy, sunlight, lubricants
- penicillin V or erythromycin if Group A β-hemolytic Streptococcus on throat culture

3. ERYTHRODERMIC PSORIASIS

Clinical Presentation
- generalized erythema (> 90% of body surface area) with fine desquamative scale on surface
- associated signs and symptoms: arthralgia, pruritus, dehydration, electrolyte imbalance
- aggravating factors: lithium, β-blockers, NSAIDs, antimalarials, phototoxic reaction, infection

Management
- IV fluids, monitor fluids and electrolytes, may require hospitalization
- treat underlying aggravating condition, sun avoidance
- cyclosporine, acitretin, UV, biologics

4. PUSTULAR PSORIASIS

Clinical Presentation
- sudden onset of erythematous macules and papules which evolve rapidly into pustules, can be painful
- may be generalized or localized to palms/soles
- patient usually has a history of psoriasis; may occur with sudden withdrawal from steroid therapy
5. INVERSE PSORIASIS

Clinical Presentation
• erythematous plaques on flexural surfaces such as axillae, inframammary folds, gluteal fold, inguinal folds
• lesions may be macerated

Management
• low potency topical corticosteroids
• topical vitamin D derivatives such as calcipotriene or calcitriol
• topical calcineurin inhibitors such as tacrolimus or pimecrolimus

6. PSORIATIC ARTHRITIS

• 5-30% of patients with psoriasis can also be suffering from psoriatic arthritis
• psoriatic patients with nail or scalp involvement are at a higher risk for developing psoriatic arthritis
• see Rheumatology, RH23

Vesiculobullous Diseases

Bullous Pemphigoid

Clinical Presentation
• chronic autoimmune bullous eruption characterized by pruritic, tense, subepidermal bullae on an erythematous or normal skin base
• can present as urticarial plaques without bullae
• common sites: flexor aspect of forearms, axillae, medial thighs, groin, abdomen, mouth in 33%

Pathophysiology
• IgG produced against dermal-epidermal basement membrane proteins (hemidesmosomes) leads to subepidermal bullae

Epidemiology
• mean age of onset: 60-80 yr old, F=M

Investigations
• immunofluorescence shows linear deposition of IgG and C3 along the basement membrane
• anti-basement membrane antibody (IgG) (pemphigoid antibody detectable in serum)

Prognosis
• heals without scarring, usually chronic
• rarely fatal

Management
• prednisone 0.5-1 mg/kg/day until clear, then taper ± steroid-sparing agents (e.g. azathioprine, methotrexate)
• topical potent steroids (clobetasol) may be as effective as systemic steroids in limited disease
• tetracycline ± nicotinamide is effective for some cases
• immunosuppressants such as azathioprine, mycophenolate mofetil, cyclosporine
• IVIg and plasmapheresis for refractory cases

Pemphigus Vulgaris

Clinical Presentation
• autoimmune blistering disease characterized by flaccid, non-pruritic intraepidermal bullae/vesicles on an erythematous or normal skin base
• may present with erosions and secondary bacterial infection
• sites: mouth (90%), scalp, face, chest, axillae, groin, umbilicus
• Nikolsky’s sign: rubbing pressure on skin to cause bulla formation
• Asboe-Hansen sign: pressure applied to bulla causes it to extend laterally

Pathophysiology
• IgG against epidermal desmoglein-1 and -3 leads to loss of intercellular adhesion in the epidermis
Epidemiology
• 40-60 yr old, M=F, higher prevalence in Jewish, Mediterranean, Asian populations
• paraneoplastic pemphigus may be associated with thymoma, myasthenia gravis, malignancy, and use of D-penicillamine

Investigations
• immunofluorescence: shows IgG and C3 deposition intraepidermally
• circulating serum anti-desmoglein IgG antibodies

Prognosis
• lesions heal with hyperpigmentation but do not scar
• may be fatal unless treated with immunosuppressive agents

Management
• prednisone 1-2 mg/kg until no new blisters, then 1-1.5 mg/kg until clear, then taper ± steroid-sparing agents (e.g. azathioprine, methotrexate, gold, cyclophosphamide, cyclosporine, IVlg, mycophenolate mofetil, rituximab)

Dermatitis Herpetiformis

Clinical Presentation
• grouped papules/vesicles/urticarial wheals on an erythematous base, associated with intense pruritus, burning, stinging, excoriations
• lesions grouped, bilaterally symmetrical
• common sites: extensor surfaces of elbows/knees, sacrum, buttocks, scalp

Pathophysiology
• transglutaminase IgA deposits in the skin alone or in immune complexes leading to eosinophil and neutrophil infiltration
• 90% have HLA B8, DR3, DQWZ
• 90-100% associated with an often subclinical gluten-sensitive enteropathy (i.e. celiac disease)
• 30% have thyroid disease; increased risk of intestinal lymphoma in untreated comorbid celiac disease; iron/folate deficiency is common

Epidemiology
• 20-60 yr old, M:F = 2:1

Investigations
• biopsy
• immunofluorescence shows IgA deposits in perilesional skin

Management
• dapsone (sulfapyridine if contraindicated or poorly tolerated)
• gluten-free diet for life – this can reduce risk of lymphoma

Porphyria Cutanea Tarda

Clinical Presentation
• skin fragility followed by formation of tense vesicles/bullae and erosions on photoexposed skin
• gradual healing to scars, milia
• periorbital violaceous discoloration, diffuse hypermelanosis, facial hypertrichosis
• common sites: light-exposed areas subjected to trauma, dorsum of hands and feet, nose, and upper trunk

Pathophysiology
• uroporphyrinogen decarboxylase deficiency leads to excess heme precursors
• can be associated with hemochromatosis, alcohol abuse, DM, drugs (estrogen therapy, NSAIDs), HIV, hepatitis C, increased iron indices

Epidemiology
• 30-40 yr old, M>F

Investigations
• urine + 5% HCl shows orange-red fluorescence under Wood's lamp (UV rays)
• 24 h urine for uroporphyrins (elevated)
• stool contains elevated coproporphyrins
• immunofluorescence shows IgE at dermal-epidermal junctions

Management
• discontinue aggravating substances (alcohol, estrogen therapy)
• phlebotomy to decrease body iron load
• low dose hydroxychloroquine
Drug Eruptions

Exanthematous

EXANTHEMATOUS DRUG REACTION

Clinical Presentation
• morphology: erythematous macules and papules ± scale
• spread: symmetrical, trunk to extremities
• time course: 7-14 d after drug initiation, fades 7-14 d after withdrawal

Epidemiology
• most common cutaneous drug reaction; increased in presence of infections
• common causative agents: penicillin, sulfonamides, phenytoin

Management
• weigh risks and benefits of drug discontinuation
• antihistamines, emollients, topical steroids

DRUG INDUCED HYPERSENSITIVITY SYNDROME (DIHS) / DRUG REACTION WITH EOSINOPHILIA AND SYSTEMIC SYMPTOMS (DRESS)

Clinical Presentation
• morphology: morbilliform rash involving face, trunk, arms; can have facial edema
• systemic features: fever, malaise, cervical lymphadenopathy, internal organ involvement (e.g. hepatitis, arthralgia, nephritis, pneumonitis, lymphadenopathy, hematologic abnormalities, thyroid abnormalities)
• spread: starts with face or periorbitally and spreads caudally; no mucosal involvement
• time course: 1-6 weeks after first exposure to drug, persists weeks after withdrawal of drug

Epidemiology
• rare: incidence varies considerably depending on drug
• common causative agents: anticonvulsants (e.g. phenytoin, phenobarbital, carbamazepine, lamotrigine), sulfonamides, and allopurinol
• 10% mortality if severe, undiagnosed, and untreated

Management
• discontinue offending drug ± prednisone 0.5mg/kg per day, consider cyclosporine in severe cases
• may progress to generalized exfoliative dermatitis/erythroderma if drug is not discontinued

Urticarial

DRUG INDUCED URTICARIA AND ANGIOEDEMA

Clinical Presentation
• morphology: wheals lasting <24hrs, angioedema (face and mucous membranes)
• systemic features: may be associated with systemic anaphylaxis (bronchospasm, laryngeal edema, shock)
• time course: hours to days after exposure depending on the mechanism

Epidemiology
• second most common cutaneous drug reaction
• common causative agents: penicillins, ACEI, analgesics/anti-inflammatories, radiographic contrast media

Management
• discontinue offending drug, antihistamines, steroids, epinephrine if anaphylactic

Diagnosis of a Drug Reaction
Classification by Naranjo et. al has 4 criteria:
1. Temporal relationship between drug exposure and reaction
2. Recognized response to suspected drug
3. Improvement after drug withdrawal
4. Recurrence of reaction on re-challenge with the drug

Definite drug reaction requires all 4 criteria to be met
Probable drug reaction requires #1-3 to be met
Possible drug reaction requires only #1
SERUM SICKNESS-LIKE REACTION

Clinical Presentation
• morphology: symmetrical cutaneous eruption (usually urticarial)
• systemic features: malaise, low grade fever, althralgia, lymphadenopathy
• time course: appears 1-3 wks after drug initiation, resolve 2-3 wks after withdrawal

Epidemiology
• more prevalent in kids 0.02-0.2%
• common causative agents: cefaclor in kids; buproprion in adults

Management
• discontinue offending drug ± topical/oral corticosteroids

Pustular

ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS (AGEP)

Clinical Presentation
• morphology: erythematous edema and sterile pustules prominent in intertriginous areas
• systemic features: high fever, leukocytosis with neutrophilia
• spread: starts in face and intertriginous areas and spread to trunk and extremities
• time course: appears 1 wk after drug initiation, resolve 2 wks after withdrawal

Epidemiology
• rare: 1-5/million
• common causative agents: aminopenicillins, cephalosporins, clindamycin, calcium channel blockers

Management
• discontinue offending drug and systemic corticosteroids

Bullous

STEVEN-JOHNSON SYNDROME (SJS)/TOXIC EPIDERMAL NECROLYSIS (TEN)

Clinical Presentation
• morphology: prodromal rash (morbilliform/targetoid lesions ± purpura, or diffuse erythema), confluence of flaccid blisters, positive Nikolsky sign (epidermal detachment with shear stress), full thickness epidermal loss;
• classification: BSA with epidermal detachment: <10% in SJS, 10-30% in SJS/TEN overlap, and >30% in TEN
• spread: face and extremities; may generalize; scalp, palms, soles relatively spared; erosion of mucous membranes (lips, oral mucosa, conjunctiva, GU mucosa)
• systemic features: fever (higher in TEN), cytopenias, renal tubular necrosis/AKI, tracheal erosion, infection, contractures, corneal scarring, phimosis, vaginal synchieae
• time course: appears 1-3 wk after drug initiation; progression <4days; epidermal regrowth in 3wk

Epidemiology
• SJS: 1.2-6/million; TEN: 0.4-1.2/million
• risk factors: SLE, HIV/AIDS, HLA-B1502 (associated with carbamazepine), HLA-B5801 (associated with allopurinol)
• common causative agents: drugs (allopurinol, anti-epileptics, sulfonamides, NSAIDs, cephalosporins) responsible in 50% of SJS and 80% of TEN; viral or mycoplasma infections;
• prognosis: 5% mortality in SJS, 30% in TEN due to fluid loss & infection

Differential Diagnosis
• Scarlet fever, phototoxic eruption, GVHD, SSSS, exfoliative dermatitis, AGEP, paraneoplastic pemphigus

Management
• discontinue offending drug
• admit to intermediate/intensive care/burn unit
• supportive care: IV fluids, electrolyte replacement, nutritional support, pain control, wound care, sterile handling, monitor for and treat infection
• IVIG or cyclosporine

SCORTEN Score for TEN Prognosis

One point for each of: age ≥40, malignancy, body surface area detached ≥10%, tachycardia ≥120 bpm, serum urea >10 mmol/L, serum glucose >14 mmol/L, serum bicarbonate <20 mmol/L

Used to determine appropriate clinical setting: score 0-1 can be treated in non-specialized wards; score ≥2 should be transferred to intensive care or burn unit

Score at admission is predictive of survival: 94% for 0-1, 87% for 2, 53% for 3, 25% for 4, and 17% for ≥5
Other

FIXED DRUG ERUPTION

Clinical Presentation
- morphology: sharply demarcated erythematous oval patches on the skin or mucous membranes
- spread: commonly face, mucosa, genitalia, acral; recurs in same location upon subsequent exposure to the drug (fixed location)

Epidemiology
- common causative agents: antimicrobials (tetracycline, sulfonamides), anti-inflammatory, psychoactive agents (barbiturates), phenolphthalein

Management
- discontinue offending drug ± prednisone 1mg/kg/d x 2 wk for generalized lesions ± potent topical corticosteroids for non-eroded lesions or antimicrobial ointment for eroded lesions

PHOTOSENSITIVITY REACTION

Clinical Presentation
- phototoxic reaction: “exaggerated sunburn” (erythema, edema, vesicles, bullae) confined to sun-exposed areas
- photoallergic reaction: pruritic eczematous eruption with papules, vesicles, scaling, and crusting that may spread to areas not exposed to light

Pathophysiology
- phototoxic reaction: direct tissue injury
- photoallergic reaction: type IV delayed hypersensitivity

Epidemiology
- common causative agents: chlorpromazine, doxycycline, thiazide diuretics, procainamide

Management
- sun protection ± topical/oral corticosteroids

Heritable Disorders

Ichthyosis Vulgaris

Clinical Presentation
- xerosis with fine scaling as well as large adherent scales (“fish-scales”)
- affects arms, legs, palms, soles, back, forehead, and cheeks; spares flexural creases
- improves in summer, with humidity, and as the child grows into adulthood

Pathophysiology
- genetic deficiency in filaggrin protein leads to abnormal retention of keratinocytes (hyperkeratosis)
- scaling without inflammation

Epidemiology
- 1:300 incidence
- autosomal dominant inheritance
- associated with AD and keratosis pilaris

Investigations
- electron microscopy: keratohyalin granules

Management
- immersion in bath and oils followed by an emollient cream, humectant cream, or creams/oil containing urea or α- or β-hydroxy acids
- intermittent systemic retinoids for severe cases
Neurofibromatosis (Type I; von Recklinghausen’s Disease)

Clinical Presentation
- diagnostic criteria includes 2 or more of the following
  1. more than 5 café-au-lait patches >1.5 cm in an adult or more than 5 café-au-lait macules >0.5 cm in a child under 5 yr
  2. axillary or inguinal freckling
  3. iris hamartomas (Lisch nodules)
  4. optic gliomas
  5. neurofibromas
  6. distinctive bony lesion (sphenoid wing dysplasia or thinning of long bone cortex)
  7. first degree relative with neurofibromatosis type 1
- associated with pheochromocytoma, astrocytoma, bilateral acoustic neuromas, bone cysts, scoliosis, precocious puberty, developmental delay, and renal artery stenosis
- skin lesions less prominent in neurofibromatosis Type II (see Pediatrics, P86)

Pathophysiology
- autosomal dominant disorder with excessive and abnormal proliferation of neural crest elements (Schwann cells, melanocytes), high incidence of spontaneous mutation
- linked to absence of neurofibromin (a tumour suppressor gene)

Epidemiology
- incidence 1:3,000

Investigations
- Wood's lamp examination to detect café-au-lait macules in patients with pale skin

Management
- refer to orthopedics, ophthalmology, plastics, and psychology for relevant management
- follow-up annually for brain tumours such as astrocytoma
- excise suspicious or painful lesions
- see Pediatrics, P86

Vitiligo

Clinical Presentation
- primary pigmentary disorder characterized by depigmentation
- acquired destruction of melanocytes characterized by sharply margined white patches
- associated with streaks of depigmented hair, chorioretinitis
- sites: extensor surfaces and periorificial areas (mouth, eyes, anus, genitalia)
- Koebner phenomenon, may be precipitated by trauma

Pathophysiology
- acquired autoimmune destruction of melanocytes

Epidemiology
- 1% incidence, polygenic
- 30% with positive family history

Investigations
- rule out associated autoimmune diseases: thyroid disease, pernicious anemia, Addison’s disease, Type I DM
- Wood's lamp to detect lesions: illuminates UV light onto skin to detect amelanosis (porcelain white discolouration)

Management
- sun avoidance and protection
- topical calcineurin inhibitor (e.g. tacrolimus, pimecrolimus) or topical corticosteroids
- PUVA or Narrow band UVB
- make-up
- “bleaching” normal pigmented areas (i.e. monobenzyl ether of hydroquinone 20%) if widespread loss of pigmentation

Interventions for Vitiligo
Cochrane DB Syst Rev 2010;1:CD003263
Study: Systematic review of randomized controlled trials.
Patients: 3,139 participants with vitiligo.
Intervention: Topical treatments, light therapies, oral treatments, surgical methods, and psychological therapies
Outcome: >75% repigmentation, adverse effects
Results: Moderate evidence exists for the use of topical corticosteroids to induce repigmentation but, adverse effects are observed with long-term use. Topical use of non-steroidal immunomodulators (e.g. tacrolimus), especially in combination with light therapies, has also been shown to induce repigmentation, but long-term use may theoretically increase the risk for skin cancer. In general, combination therapy including some form of light therapy had the most significant improvement. Sustained repigmentation (>2 yr) has not been reported and thus results should be treated with caution.
Bacterial Infections

EPIDERMIS

IMPETIGO

Clinical Presentation
- acute purulent infection which appears vesicular; progresses to golden yellow “honey-crusted” lesions surrounded by erythema
- can present with bullae
- common sites: face, arms, legs, and buttocks

Etiology
- GAS, S. aureus, or both

Epidemiology
- preschool and young adults living in crowded conditions, poor hygiene, neglected minor trauma

Differential Diagnosis
- infected eczema, HSV, VZV

Investigations
- Gram stain and culture of lesion fluid or biopsy

Management
- remove crusts, use saline compresses, and topical antiseptic soaks bid
- topical antibacterials such as 2% mupirocin or fusidic acid (Canada only) tid; continue for 7-10 d after resolution
- systemic antibiotics such as cloxacillin or cephalaxin for 7-10 d

Figure 7. Layers of skin affected by bacterial infections

Location Matters!
- Impetigo → just below stratum corneum
- Erysipelas → epidermis and upper dermis only
- Cellulitis → primarily lower dermis and subcutis (primarily not raised, and demarcation less distinct than erysipelas)
- Necrotizing fasciitis → deep fascia and muscle
Table 16. Comparison of Erysipelas and Cellulitis

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Etiology</th>
<th>Complications</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erysipelas</td>
<td>GAS</td>
<td>Scarlet fever, streptococcal gangrene, fat necrosis, coagulopathy</td>
<td>DVT (less red, less hot, smoother), superficial phlebitis, contact dermatitis, photosensitivity reaction, stasis dermatitis, panniculitis, vasculitis</td>
<td>Clinical diagnosis: rarely do skin/blood culture If suspect necrotizing fasciitis: do immediate biopsy and frozen section, histopathology</td>
<td>1st line: penicillin, clindamycin or cefazolin 2nd line: clindamycin or cephalexin 1st line: gentamicin or tobramycin 2nd line: clindamycin or cephalexin If allergic to penicillin, use erythromycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>GAS, S. aureus (large sized wounds), H. influenzae (periorbital), Pasteurella multocida (dog/cat bite)</td>
<td>Uncommon</td>
<td>Same as erysipelas</td>
<td>Same as erysipelas</td>
<td>1st line: clindamycin or cefazolin 2nd line: clindamycin or cephalexin Children: cefuroxime If DM (foot infections): TMP/SMX and metronidazole</td>
</tr>
</tbody>
</table>

Table 17. Comparison of Superficial Folliculitis, Furuncles, and Carbuncles

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial Folliculitis</td>
<td>Normal non-pathogenic bacteria (Staphylococcus – most common; Pseudomonas – hot tub) Pityrosporum</td>
<td>Antiseptic (Hibiclens®) Topical antibacterial (fusidic acid, mupirocin, erythromycin or clindamycin) Oral clindamycin for 7-10 d</td>
</tr>
<tr>
<td>Furuncles (Boils)</td>
<td>S. aureus</td>
<td>Incise and drain large furuncles to relieve pressure and pain If afebrile: hot wet packs, topical antibiotic If febrile/cellulitis: culture blood and aspirate pustules (Gram stain and C&amp;S) Clindamycin for 1-2 wk (especially for lesions near external auditory canal/nose, with surrounding cellulitis, and not responsive to topical therapy)</td>
</tr>
<tr>
<td>Carbuncles</td>
<td>S. aureus</td>
<td>Same as for furuncles</td>
</tr>
</tbody>
</table>

**Dermatophytoses**

**Clinical Presentation**
- infection of skin, hair, and nails caused by dermatophytes (fungi that live within the epidermal keratin or hair follicle and do not penetrate into deeper structures)

**Pathophysiology**
- digestion of keratin by dermatophytes results in scaly skin, broken hairs, crumbling nails/onycholysis

**Etiology**
- *Trichophyton, Microsporum, Epidermophyton* species (*Pityrosporum* is a superficial yeast and not a dermatophyte)

**Investigations**
- skin scrapings, hair, and/or nail clippings analyzed with potassium hydroxide (KOH) prep to look for hyphae and mycelia
### Management
- Topicals as first line agents for tinea corporis/cruris and tinea pedis (interdigital type): clotrimazole, or terbinafine or ciclopirox olamine cream applied bid
- Oral therapy is indicated for onychomycosis or tinea capitis: terbinafine (Lamisil® – liver toxicity, CYP2D6 inhibitor) or itraconazole (Sporanox® – CYP3A4 inhibitor, liver toxicity)

### Table 18. Different Manifestations of Dermatophyte Infection

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Differential Diagnosis</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tinea Capitis</strong></td>
<td>Round, scaly patches of alopecia, possibly with broken off hairs; pruritic</td>
<td>Alopecia areata, psoriasis, seborrheic dermatitis, trichotillomania</td>
<td>Wood’s light examination of hair: green fluorescence only for Microsporum infection Culture of scales/hair shaft Microscopic examination of KOH preparation of scales or hair shafts</td>
</tr>
<tr>
<td><strong>Tinea Corporis</strong> (Ringworm)</td>
<td>Pruritic, scaly, round/oval plaque with active erythematous margin, and central clearing Site: trunk, limbs, face</td>
<td>Granuloma annulare, pityriasis rosea, psoriasis, seborrheic dermatitis</td>
<td>Microscopic examinations of KOH prep of scales shows hyphae Culture of scales</td>
</tr>
<tr>
<td><strong>Tinea Cruris</strong> (“Jock Itch”)</td>
<td>Scaly patch/plaque with a well-defined, curved border and central clearing</td>
<td>Candidiasis (involvement of scrotum and satellite lesions), contact dermatitis, erythrasma</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td><strong>Tinea Pedis</strong> (Athlete’s Foot)</td>
<td>Pruritic scaling and/or maceration of the web spaces, and powdery scaling of soles Acute infection: interdigital (esp. 4th web space) red/white scales, vesicles, bullae, often with maceration Secondary bacterial infection may occur Chronic: non-pruritic, pink, scaling keratosis on soles and sides of feet May present as flare-up of chronic tinea pedis Predisposing factors: heat, humidity, occlusive footwear</td>
<td>AD, contact dermatitis, dyshidrotic dermatitis, erythrasma, intertrigo, inverse psoriasis</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td><strong>Tinea Mannum</strong></td>
<td>Primary fungal infection of the hand is rare; usually associated with tinea pedis Acute: blisters at edge of red areas on hands Chronic: single dry scaly patch</td>
<td>AD, contact dermatitis, granuloma annulare, psoriasis</td>
<td>Same as for tinea corporis</td>
</tr>
<tr>
<td><strong>Tinea Unguium</strong> (Onychomycosis)</td>
<td>Crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris Toenail infections usually precede fingernail infections T. rubrum (90% of all toenail infections)</td>
<td>Psoriasis, lichen planus, contact dermatitis, traumatic onychodystrophies, bacterial infections</td>
<td>Microscopic examinations of KOH prep of scales from subungual scraping shows hyphae Culture of subungual scraping or nail clippings on Sabouraud’s agar PAS stain of nail clipping by pathology</td>
</tr>
</tbody>
</table>

### Parasitic Infections

#### SCABIES

**Clinical Presentation**
- Characterized by superficial burrows, intense pruritus (especially nocturnal), and secondary infection
- Primary lesion: superficial linear burrows; inflammatory papules and nodules in the axilla and groin
- Secondary lesion: small urticarial crusted papules, eczematous plaques, excoriations
- Common sites: axillae, groin, buttocks, hands/feet (especially web spaces), sparing of head and neck (except in infants)
**Pathophysiology**
- scabies mite remains alive 2-3 d on clothing/sheets
- incubation of 1 mo, then pruritus begins
- re-infection followed by hypersensitivity in 24 h

**Etiology**
- *Sarcoptes scabiei* (a mite)
- risk factors: sexual promiscuity, crowding, poverty, nosocomial, immunocompromised

**Differential Diagnosis**
- asteatotic eczema, dermatitis herpetiformis, lichen simplex chronicus (neurodermatitis)

**Investigations**
- microscopic examination of root and content of burrow and mineral oil mount for mite, eggs, feces
- skin biopsy may sometimes show scabies mite

**Management**
- bathe, then apply permethrin 5% cream (i.e. Nix®) from neck down to soles of feet (must be left on for 8-14 h and requires second treatment 7 d after first treatment)
- change underwear and linens; wash twice with detergent in hot water cycle then machine dry
- treat family and close contacts
- pruritus may persist for 2-3 wk after effective treatment due to prolonged hypersensitivity reaction
- mid potency topical steroids and antihistamines for symptom management

**LICE (PEDICULOSIS)**

**Clinical Presentation**
- intensely pruritic red excoriations, morbilliform rash, caused by louse (a parasite)
- scalp lice: nits (i.e. louse eggs) on hairs; red, excoriated skin with secondary bacterial infection, lymphadenopathy
- pubic lice: nits on hairs; excoriations
- body lice: nits and lice in seams of clothing; excoriations and secondary infection mainly on shoulders, belt-line and buttocks

**Etiology**
- *Phthirius pubis* (pubic), *Pediculus humanus capitis* (scalp), *Pediculus humanus humanus* (body): attaches to body hair and feeds
- can transmit infectious agents such as *Bartonella quintana* and *Rickettsia prowazekii*

**Differential Diagnosis**
- bacterial infection of scalp, seborrheic dermatitis

**Diagnosis**
- lice visible on inspection of affected area or clothing seams

**Management**
- permethrin 1% (Nix® cream rinse) (ovicidal) or permethrin 1% (RC & Cor®, Kwella-P® shampoo)
- comb hair with fine-toothed comb using dilute vinegar solution to remove nits
- repeat in 7 d after first treatment
- shave hair if feasible, change clothing and linens; wash with detergent in hot water cycle then machine dry

**BED BUGS (HEMIPTERA)**

**Clinical Presentation**
- burning wheals, turning to firm papules, often in groups of three – “breakfast, lunch and dinner” – in areas with easy access (face, neck, arms, legs, hands)

**Etiology**
- caused by *Cimex lectularius*, a small insect that feeds mainly at night (hide in crevices in walls and furniture during the day)

**Differential Diagnosis**
- dermatitis herpetiformis, drug eruptions, ecthyma, other insect bites, scabies

**Investigations**
- none required, but lesional biopsy can confirm insect bite reaction

**Management**
- professional fumigation
- topical steroids and oral H1-antagonists for symptomatic relief
- definitive treatment is removal of clutter in home and application of insecticides to walls and furniture
**Viral Infections**

**HERPES SIMPLEX**

**Clinical Presentation**
- herpetiform (i.e. grouped) vesicles on an erythematous base on skin or mucous membranes
- transmitted via contact with erupted vesicles or via asymptomatic viral shedding
- **primary**
  - children and young adults
  - usually asymptomatic; may have high fever, regional lymphadenopathy, malaise
  - followed by antibody formation and latency of virus in dorsal nerve root ganglion
- **secondary**
  - recurrent form seen in adults; much more common than primary
  - prodrome: tingling, pruritus, pain
  - triggers for recurrence: fever, excess sun exposure, physical trauma, menstruation, emotional stress, URTI
- **complications**: dendritic corneal ulcer, EM, herpes simplex encephalitis (infants at risk), HSV infection on AD causing Kaposi's varicelliform eruption (eczema herpeticum)
- two biologically and immunologically different subtypes: HSV-1 and HSV-2
  - HSV-1
    - typically “cold sores” (grouped vesicles at the mucocutaneous junction which quickly burst)
    - recurrent on face, lips and hard palate, but NOT on soft, non-keratinized mucous membranes (unlike aphthous ulcers)
  - HSV-2
    - usually sexually transmitted; incubation 2-20 d
    - gingivostomatitis: entire buccal mucosa involved with erythema and edema of gingiva
    - vulvovaginitis: edematous, erythematous, extremely tender, profuse vaginal discharge
    - urethritis: watery discharge in males
    - recurrent on vulva, vagina, penis for 5-7 d
- differential diagnosis of genital ulcers: Candida balanitis, chancroid, syphilitic chancres

**Investigations**
- Tzanck smear with Giemsa stain shows multinucleated giant epithelial cells
- viral culture, electron microscopy, and direct fluorescence antibody test of specimen taken from the base of a relatively new lesion
- serologic testing for antibody for current or past infection if necessary

**Management**
- HSV-1
  - treat during prodrome to prevent vesicle formation
  - topical antiviral (Zovirax®/Xerese®) cream, apply 5-6x/d x 4-7 d for facial/genital lesions
  - oral antivirals (e.g. acyclovir, famciclovir, valacyclovir) are far more effective and have an easier dosing schedule than topicals
- HSV-2
  - rupture vesicle with sterile needle if you wish to culture it
  - wet dressing with aluminum subacetate solution, Burow’s compression, or betadine solution
  - 1st episode: acyclovir 200 mg PO 5x/d x 10 d
  - maintenance: acyclovir 400 mg PO bid
  - famciclovir and valacyclovir may be substituted and have better enteric absorption and less frequent dosing
  - in case of herpes genitalis, look for and treat any other sexually-transmitted infections STIs
  - for active lesions in pregnancy, see Obstetrics, OB30

**HERPES ZOSTER (SHINGLES)**

**Clinical Presentation**
- unilateral dermatomal eruption occurring 3-5 d after pain and paresthesia of that dermatome
- vesicles, bullae, and pustules on an erythematous, edematous base
- lesions may become eroded/ulcerated and last days to weeks
- pain can be pre-herpetic, synchronous with rash, or post-herpetic
- severe post-herpetic neuralgia often occurs in elderly
- Hutchinson’s sign: Shingles on the tip of the nose signifies eye involvement. Shingles in this area involves the nasociliary branch of the ophthalmic branch of the trigeminal nerve, which is why it signals a high risk for ocular involvement
- distribution: thoracic (50%), trigeminal (10-20%), cervical (10-20%); disseminated in HIV

**Etiology**
- caused by reactivation of VZV
- risk factors: immunosuppression, old age, occasionally associated with hematologic malignancy

**Differential Diagnosis**
- before thoracic skin lesions occur, must consider other causes of chest pain
- contact dermatitis, localized bacterial infection, zosteriform HSV (more pathogenic for the eyes than VZV)
Investigations
• none required, but can do Tzanck test, direct fluorescence antibody test, or viral culture to rule out HSV

Management
• compress with normal saline, Burow’s, or betadine solution
• analgesics (NSAIDs, amitriptyline)
• famciclovir, valacyclovir, or acyclovir for 7 d; must initiate within 72 h to be of benefit
• gabapentin 300-600 mg PO tid for post-herpetic neuralgia

MOLLUSCUM CONTAGIOSUM

Clinical Presentation
• discrete dome-shaped and umbilicated pearly, white papules caused by DNA Pox virus (Molluscum contagiosum virus)
• common sites: eyelids, beard (likely spread by shaving), neck, axillae, trunk, perineum, buttocks

Etiology
• virus is spread via direct contact, auto-inoculation, sexual contact
• common in children and sexually active young adults (giant molluscum and severe cases can be seen in the setting of HIV)

Investigations
• none required, however can biopsy to confirm diagnosis

Management
• topical cantharidin (a vesicant)
• cryotherapy
• curettage
• topical retinoids
• Aldara® (imiquimod): immune modulator that produces a cytokine inflammation

WARTS (VERRUCA VULGARIS) (HUMAN PAPILLOMAVIRUS INFECTIONS)

Table 19. Different Manifestations of HPV Infection

<table>
<thead>
<tr>
<th>Definition and Clinical Features</th>
<th>Differential Diagnosis</th>
<th>Distribution</th>
<th>HPV Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verruca Vulgaris (Common Warts)</td>
<td>Hyperkeratotic, elevated discrete epithelial growths with papillated surface caused by HPV Paring of surface reveals punctate, red-brown specs (thrombosed capillaries)</td>
<td>Molluscum contagiosum, seborheic keratosis</td>
<td>Located at trauma sites: fingers, hands, knees of children and teens</td>
</tr>
<tr>
<td>Verruca Plantaris (Plantar Warts) and Verruca Palmaris (Palmar Warts)</td>
<td>Hyperkeratotic, shiny, sharply marginated growths Paring of surface reveals red-brown specs (capillaries), interruption of epidermal ridges</td>
<td>May need to scrape (“pare”) lesions to differentiate wart from callus and corn</td>
<td>Located at pressure sites: metatarsal heads, heels, toes</td>
</tr>
<tr>
<td>Verruca Planae (Flat Warts)</td>
<td>Multiple discrete, skin coloured, flat topped papules grouped or in linear configuration Common in children</td>
<td>Syringoma, seborheic keratosis, molluscum contagiosum, lichen planus</td>
<td>Sites: face, dorsa of hands, shins, knees</td>
</tr>
<tr>
<td>Condyloma Acuminata (Genital Warts)</td>
<td>Skin-coloured pinhead papules to soft cauliflower like masses in clusters Often occurs in young adults, infants, children Can be asymptomatic, lasting months to years Highly contagious, transmitted sexually and non-sexually (e.g. Koebner phenomenon via scratching, shaving), and can spread without clinically apparent lesions Investigations: aceto whitening (subclinical lesions seen with 5% acetic acid x 5 min and hand lens) Complications: fairy-ring warts (satellite warts at periphery of treated area of original warts)</td>
<td>Condyloma lata (secondary syphilitic lesion, dark field strongly +ve), molluscum contagiosum</td>
<td>Sites: genitalia and perianal areas</td>
</tr>
</tbody>
</table>

Treatment for Warts
• first line therapies
  • salicylic acid preparations (patches, solutions, creams, ointments), cryotherapy, topical cantharone
• second line therapies
  • topical imiquimod, topical 5-fluorouracil, topical tretinoin, podophyllotoxin
• third line therapies
  • curettage, cautery, surgery for non plantar warts, CO2 laser, oral cimetidine (particularly children), intralesional bleomycin (plantar warts), trichloroacetic acid, diphenycrynone
• other viruses associated with skin changes, such as measles, roseola, fifth disease, etc.
• see Pediatrics, Pediatric Exanthems, P56
Yeast Infections

CANDIDIASIS

Etiology
• many species of Candida (70-80% of infections are from Candida albicans)
• opportunistic infection in those with predisposing factors (e.g. trauma, malnutrition, immunodeficiency)

Candidal Paronychia
• clinical presentation: painful red swellings of periungual skin
• management: topical agents not as effective; oral antifungals recommended

Candidal Intertrigo
• clinical presentation:
  • macerated/eroded erythematous patches that may be covered with papules and pustules, located in intertriginous areas often under breast, groin, or interdigitally
  • peripheral “satellite” pustules
  • starts as non-infectious maceration from heat, moisture, and friction
• predisposing factors: obesity, DM, systemic antibiotics, immunosuppression, malignancy
• management: keep area dry, terbinafine, ciclopirox olamine, ketoconazole/clotrimazole cream bid until rash clears

PITYRIASIS (TINEA) VERSICOLOR

Clinical Presentation
• asymptomatic superficial fungal infection with brown/white scaling macules
• affected skin darker than surrounding skin in winter, lighter in summer (does not tan)
• common sites: upper chest and back

Pathophysiology
• microbe produces azelaic acid → inflammatory reaction inhibiting melanin synthesis yielding variable pigmentation
• affinity for sebaceous glands; require fatty acids to survive

Etiology
• Pityrosporum ovale (Malassezia furfur)
• also associated with folliculitis and seborrheic dermatitis
• predisposing factors: summer, tropical climates, excessive sweating, Cushing’s syndrome, prolonged corticosteroid use

Investigations
• clinical diagnosis but can perform microscopic examination, KOH prep of scales for hyphae and spores

Management
• ketoconazole shampoo or cream daily
• topical terbinafine or ciclopirox olamine bid
• systemic fluconazole or itraconazole for 7 d if extensive

Sexually Transmitted Infections

SYPHILIS

Clinical Presentation
• characterized initially by a painless ulcer (chancre)
• following inoculation, systemic infection with secondary and tertiary stages

Etiology
• Treponema pallidum
• transmitted sexually, congenitally, or rarely by transfusion
**Table 20. Stages of Syphilis**

<table>
<thead>
<tr>
<th>Clinical Presentation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Syphilis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Single red, indurated, painless chancre, that develops into painless ulcer with raised border and scanty serous exudate</td>
<td>CAN NOT be based on clinical presentation alone</td>
<td>Penicillin G, 2.4 million units IM, single dose</td>
</tr>
<tr>
<td>Chancre develops at site of inoculation after 3 wk of incubation and heals in 4-6 wk; chancre may also develop on lips or anus</td>
<td>VDRL negative – repeat weekly for 1 mo</td>
<td></td>
</tr>
<tr>
<td>Regional non-tender lymphadenopathy appears &lt; 1 wk after onset of chancre</td>
<td>Fluorescent treponemal antibody-syphilis (FTA-ABS) test has greater sensitivity and may detect disease earlier in course</td>
<td></td>
</tr>
<tr>
<td>DDx: chancroid (painful), HSV (multiple lesions)</td>
<td>Dark field examination – spirochete in chancre fluid or lymph node aspirate</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Syphilis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Presents 2-6 mo after primary infection (patient may not recall presence of primary chancre)</td>
<td>VDRL positive</td>
<td>As for primary syphilis</td>
</tr>
<tr>
<td>Associated with generalized lymphadenopathy, splenomegaly, headache, chills, fever, arthralgias, myalgia, malaise, photophobia</td>
<td>FTA-ABS +ve; –ve after 1 yr following appearance of chancre</td>
<td></td>
</tr>
<tr>
<td>Lesions heal in 1-5 wk and may recur for 1 yr</td>
<td>Dark field +ve in all secondary</td>
<td></td>
</tr>
<tr>
<td>3 types of lesions:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Macules and papules: flat top, scaling, non-pruritic, sharply defined, circular/annular rash (DDx: pityriasis rosea, tinea corporis, drug eruptions, lichen planus)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Condyloma lata: wart-like moist papules around genital/perianal region</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Mucous patches: macerated patches mainly found in oral mucosa</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Tertiary Syphilis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extremely rare</td>
<td>As in primary syphilis, VDRL can be falsely negative</td>
<td>Treatment: penicillin G, 2.4 million units IM weekly x 3 wk</td>
</tr>
<tr>
<td>3-7 yr after secondary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main skin lesion: ‘Gumma’ – a granulomatous non-tender nodule</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**GONOCOCCEMIA**

**Clinical Presentation**
- disseminated gonococcal infection
- hemorrhagic, tender, pustules on a purpuric/petechial background
- common sites: distal aspects of extremities
- associated with fever, arthritis, urethritis, proctitis, pharyngitis, and tenosynovitis
- neonatal conjunctivitis if infected via birth canal

**Etiology**
- *Neisseria gonorrhoeae*

**Investigations**
- requires high index of clinical suspicion plays because tests are often negative
- bacterial culture of blood, joint fluid, and skin lesions
- joint fluid cell count and Gram stain

**Management**
- notify Public Health authorities
- screen for other STIs
- cefixime 400 mg PO (drug of choice) or ceftriaxone 125 mg IM

**HSV**
- see *Viral Infections, D30*

**HPV**
- see *Viral Infections, D31*
Pre-Malignant Skin Conditions

Actinic Keratosis (Solar Keratosis)

Clinical Presentation
- ill-defined, scaly erythematous papules or plaques on a background of sun-damaged skin (solar heliosis)
- sandpaper-like, gritty sensation felt on palpation, often easier to appreciate on palpation rather than inspection
- sites: areas of sun exposure (face, ears, scalp if bald, neck, sun-exposed limbs)

Pathophysiology
- UV radiation damage to keratinocytes from repeated sun exposure (especially UVB)
- risk of transformation of AK to SCC (~1/1,000), but higher likelihood if AK is persistent

Epidemiology
- common with increasing age, outdoor occupation, M>F
- skin phototypes I-III, rare in darker skin as melanin is protective

Differential Diagnosis
- SCC in situ, superficial BCC, seborrheic keratosis, cutaneous lupus erythematosus

Investigations
- biopsy lesions that are refractory to treatment

Management
- destructive: cryotherapy, electrodesiccation, and curettage
- topical pharmacotherapy (mechanism: destruction of rapidly growing cells or immune system modulation)
  - topical 5-Fluorouracil cream (for 2-4 wk), Imiquimod 5% (2 times per wk for 16 wk), Imiquimod 3.75% (daily for 2 wk then none for 2 wk then daily for 2 wk), Ingenol Mebutate gel 0.015% (daily for 3 d on the head and neck), Ingenol mebutate 0.05% gel (daily for 2 d on the body)
- photodynamic therapy
- excision

Types of AK
- Erythematous: typical AK lesion
- Hypertrophic: thicker, rough papule/plaque
- Cutaneous horn: firm hyperkeratotic outgrowth
- Actinic cheilitis: confluent AKs on the lip
- Pigmented: flat, tan-brown, scaly plaque
- Spreading pigmented
- Proliferative
- Conjunctival: pinguecula, pterygium

Leukoplakia

Clinical Presentation
- a morphologic term describing homogenous or speckled white plaques with sharply demarcated borders
- sites: oropharynx, most often floor of the mouth, soft palate, and ventral/lateral surfaces of the tongue

Pathophysiology
- precancerous or premalignant condition
- oral form is strongly associated with tobacco use and alcohol consumption

Epidemiology
- 1-5% prevalence in adult population after 30 yr of age; peak at age 50
- M>F, fair-skinned
- most common oral mucosal premalignant lesion

Differential Diagnosis
- lichen planus, oral hairy leukoplakia

Investigations
- biopsy is mandatory because it is premalignant

Management
- low risk sites on buccal/labial mucosal or hard palate: eliminate carcinogenic habits, follow-up
- moderate/dysplastic lesions: excision, cryotherapy
Malignant Skin Tumours

Non-Melanoma Skin Cancers

BASAL CELL CARCINOMA

Subtypes
- noduloulcerative (typical)
  - skin-coloured papule/nodule with rolled, translucent (“pearly”) telangiectatic border, and depressed/eroded/ulcerated centre
- pigmented variant
  - flecks of pigment in translucent lesion with surface telangiectasia
- superficial variant
  - may mimic MM
- superfi
cial variant
  - flat, tan to red-brown plaque, often with scaly, pearly border and fine telangiectasia at margin
  - least aggressive subtype
- sclerosing (morpheaform) variant
  - flesh/yellowish-coloured, shiny papule/plaque with indistinct borders, indurated

Pathophysiology
- malignant proliferation of basal keratinocytes of the epidermis
- low grade cutaneous malignancy, locally aggressive (primarily tangential growth), rarely metastatic
- usually due to UVB light exposure, therefore >80% on face
- may also occur in previous scars, radiation, trauma, arsenic exposure, or genetic predisposition (Gorlin syndrome)

Epidemiology
- most common malignancy in humans
- 75% of all malignant skin tumours >40 yr, increased prevalence in the elderly
- M>F, skin phototypes I and II, chronic cumulative sun exposure

Differential Diagnosis
- benign: sebaceous hyperplasia, intradermal melanocytic nevus, dermatofibroma
- malignant: nodular MM, SCC

Management
- imiquimod 5% cream (Aldara”) or cryotherapy is indicated for superficial BCCs on the trunk
- shave excision + electrodessication and curettage for most types of BCCs, not including morpheaform
- Mohs surgery: microscopically controlled, minimally invasive, stepwise excision for lesions on the face or in areas that are difficult to reconstruct
- radiotherapy used in advanced cases of BCC where surgical intervention is not an option
- vismodegib is approved for metastatic BCC
- life-long follow-up
- 95% cure rate if lesion <2 cm in diameter or if treated early

SQUAMOUS CELL CARCINOMA

Clinical Presentation
- indurated erythematous nodule/plaque with surface scale/crust ± ulceration
- more rapid enlargement than BCC
- sites: face, ears, scalp, forearms, dorsum of hands

Pathophysiology
- malignant neoplasm of keratinocytes (primarily vertical growth)
- predisposing factors include: UV radiation, PUVA, ionizing radiation therapy/exposure, chemical carcinogens (such as arsenic, tar, and nitrogen mustards), HPV 16, 18, immunosuppression
- may occur in previous scar (SCC more commonly than BCC)

Epidemiology
- second most common type of cutaneous neoplasm
- primarily on sun-exposed skin in the elderly, M>F, skin phototypes I and II, chronic sun exposure
- in organ transplant recipients SCC is most common cutaneous malignancy, with increased mortality as compared to non-immunocompromised population
Differential Diagnosis
• benign: nummular eczema, psoriasis, irritated seborrheic keratosis
• malignant: keratoacanthoma, Bowen’s disease, BCC

Management
• surgical excision with primary closure, skin flaps or grafting
• Mohs surgery
• lifelong follow-up (more aggressive treatment than BCC)

Prognosis
• good prognostic factors: early treatment, negative margins, and small size of lesion
• SCCs that arise from AK metastasize less frequently (~1%) than other SCCs arising de novo in old burns (2-5% of cases)
• overall control is 75% over 5 yr, 5-10% metastasize

BOWEN’S DISEASE (SQUAMOUS CELL CARCINOMA IN SITU)
Clinical Presentation
• sharply demarcated erythematous plaque with scale and/or crusting
• often 1-3 cm in diameter and found on the skin and mucous membranes
• evolves to SCC in 10-20% of cutaneous lesions and >20% of mucosal lesions
Management
• same as for BCC
• biopsy required for diagnosis
• topical 5-fluorouracil (Efudex®) or imiquimod (Aldara®) used if extensive and as a tool to identify margins of poorly defined tumours
• cryosurgery
• shave excision with electrocautery and curettage

KERATOACANTHOMA
Clinical Presentation
• rapidly growing, firm, dome-shaped, erythematous or skin-coloured nodule with central keratin-filled crater, resembling an erupting volcano
• may spontaneously regress within a year, leaving a scar
• sites: sun-exposed skin
Pathophysiology
• epithelial neoplasm with atypical keratinocytes in epidermis
• low grade variant of SCC
Etiology
• HPV, UV radiation, chemical carcinogens (tar, mineral oil)
Epidemiology
• >50 yr, rare <20 yr
Differential Diagnosis
• treat as SCC until proven otherwise
• hypertrophic solar keratosis, verruca vulgaris
Management
• surgical excision or saucerization (shave biopsy) followed by electrocautery of the base, treated similarly to SCC

Malignant Melanoma
Clinical Presentation
• malignant characteristics of a mole: “ABCDE” mnemonic
• sites: skin, mucous membranes, eyes, CNS
Clinical Subtypes of Malignant Melanoma
• lentigo maligna
  • malignant melanoma in situ (normal and malignant melanocytes confined to the epidermis)
  • 2-6 cm, tan/brown/black uniformly flat macule or patch with irregular borders

Does this Patient have a Mole or Melanoma?
ABCD checklist
Asymmetry
Border (irregular and/or indistinct)
Colour (varied)
Diameter (increasing or >6 mm)
Enlargement, elevation, evolution (i.e. change in colour, size, or shape)
Sensitivity 92% (CI 82-96%)
Specificity 100% (CI 54-100%)
JAMA 1998;279:696-701
• lesion grows radially and produces complex colours
  • often seen in the elderly
  • 10% evolve to lentigo maligna melanoma
• lentigo maligna melanoma (15% of all melanomas)
  • malignant melanocytes invading into the dermis
  • associated with pre-existing solar lentigo, not pre-existing nevi
  • flat, brown, stain-like, gradually enlarging with loss of skin surface markings
  • with time, colour changes from uniform brown to dark brown with black and blue
  • found on all skin surfaces, especially those often exposed to sun, such as the face and hands
• superficial spreading melanoma (60-70% of all melanomas)
  • atypical melanocytes initially spread laterally in epidermis then invade the dermis
  • irregular, indurated, enlarging plaques with red/white/blue discolouration, focal papules or nodules
  • ulcerate and bleed with growth
• nodular melanoma (30% of all melanomas)
  • atypical melanocytes that initially grow vertically with little lateral spread
  • uniformly ulcerated, blue-black, and sharply delineated plaque or nodule
  • rapidly fatal
  • may be pink or have no colour at all, this is called an amelanotic melanoma
  • “EFG” Elevated, Firm, Growing
• acrolentiginous melanoma (5% of all melanomas)
  • ill-defined dark brown, blue-black macule
  • palmar, plantar, subungual skin
  • melanomas on mucous membranes have poor prognosis

Pathophysiology
• malignant neoplasm of pigment forming cells (melanocytes and nevus cells)

Epidemiology
• incidence 1/75 (Canada) 1/50 (US)
• risk factors: numerous moles, fair skin, red hair, positive personal/family history, large congenital nevi, familial dysplastic nevus syndrome, multiple dysplastic nevi
• most common sites: back (M), calves (F)
• worse prognosis if: male, on scalp, hands, feet, late lesion, no pre-existing nevus present

Differential Diagnosis
• benign: nevi, solar lentigo, seborrheic keratosis
• malignant: pigmented BCC

Management
• excisional biopsy preferable, otherwise incisional biopsy
• remove full depth of dermis and extend beyond edges of lesion only after histologic diagnosis
• beware of lesions that regress – tumour is usually deeper than anticipated
• high dose IFN for stage II (regional), chemotherapy (cis-platinum, BCG) and high dose IFN for stage III (distant) disease
• newer chemotherapeutic, gene therapies, and vaccines starting to be used in metastatic melanoma
• radiotherapy may be used as adjunctive treatment

Table 21. American Joint Committee on Cancer Staging System Based on Breslow’s Thickness of Invasion

<table>
<thead>
<tr>
<th>Tumour Depth</th>
<th>Stage</th>
<th>Approximate 5 Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1  1.0 mm</td>
<td>Stage I T1a – T2a</td>
<td>5-yr survival 90%</td>
</tr>
<tr>
<td>T2 1.01-2.0 mm</td>
<td>Stage II T2b – T4b</td>
<td>5-yr survival 70%</td>
</tr>
<tr>
<td>T3 2.01-4.0 mm</td>
<td>Stage III any nodes</td>
<td>5-yr survival 45%</td>
</tr>
<tr>
<td>T4  &gt;4.0 mm</td>
<td>Stage IV any mets</td>
<td>5-yr survival 10%</td>
</tr>
</tbody>
</table>

a = no ulceration; b = ulceration

Other Cutaneous Cancers

CUTANEOUS T-CELL LYMPHOMA

Clinical Presentation
• Mycosis fungoides (limited superficial type)
  • characterized by erythematous patches/plaques/nodules/tumours, which may be pruritic and poikilodermic (atrophy, telangiectasia, hyperpigmentation)
  • common sites include: trunk, buttocks, proximal limbs
  • mildly symptomatic, usually excellent prognosis for early disease
Sézary syndrome (widespread systemic type)
- rare variant characterized by erythroderma, lymphadenopathy, WBC >20 x 10^9/L with Sézary cells
- associated with intense pruritus, alopecia, palmoplantar hyperkeratosis, and systemic symptoms (fatigue, fever)
- often fatal

Pathophysiology
- clonal proliferation of skin-homing CD4 T-cells

Epidemiology
- >50 yr old, M:F 2:1

Differential Diagnosis
- tinea corporis, nummular dermatitis, psoriasis, DLE, Bowen's disease

Investigations
- skin biopsy (histology, "lymphocyte antigen cell" markers, TcR gene arrangement)
- blood smear looking for Sézary cells or flow cytometry (e.g. CD4:CD8 >10 is Sézary)
- imaging (for systemic involvement)

Management
- Mycosis fungoides
  - depends on stage of disease
  - topical steroids and/or PUVA, narrow band (311-313 nm), UVB (NBUVB)
- Sézary syndrome
  - oral retinoids and IFN
  - extra-corporeal photophoresis
  - may need radiotherapy for total skin electron beam radiation
  - may maintain on UV therapy
  - other chemotherapy agents

Diseases of Hair Density

Hair Growth
- hair grows in a cyclic pattern that is defined in 3 stages
  1. growth stage = anagen phase
  2. transitional stage = catagen stage
  3. resting stage = telogen phase
- total duration of the growth stage reflects the type and location of hair: eyebrow, eyelash, and axillary hairs have a short growth stage in relation to the resting stage
- growth of the hair follicles is also based on the hormonal response to testosterone and DHT; this response is genetically controlled

Non-Scarring (Non-Cicatricial) Alopecia

ANDROGENETIC ALOPECIA

Clinical Presentation
- male- or female-pattern alopecia
- males: fronto-temporal areas progressing to vertex, entire scalp may be bald
- females: widening of central part, “Christmas tree” pattern

Pathophysiology
- action of testosterone on hair follicles

Epidemiology
- males: early 20s-30s
- females: 40s-50s

Management
- minoxidil (Rogaine®) solution or foam to reduce rate of loss/partial restoration
- spironolactone in women (anti-androgenic effects), cyproterone acetate (Diane-35®)
- finasteride (Propecia®) (5-a-reductase inhibitor) 1 mg/d in men
- hair transplant

DDx of Non-Scarring (Non-Cicatricial) Alopecia
- Autoimmune
  - Alopecia areata
- Endocrine
  - Hypothyroidism
  - Androgens
- Micronutrient deficiencies
  - Iron
  - Zinc
- Toxins
  - Heavy metals
  - Anticoagulants
  - Chemotherapy
  - Vitamin A
- Trauma to the hair follicle
  - Trichotillomania
  - ’Corn-row’ braiding
- Other
  - Syphilis
  - Severe illness
  - Childbirth
PHYSICAL
• trichotillomania: impulse-control disorder characterized by compulsive hair pulling with irregular patches of hair loss, and with remaining hairs broken at varying lengths
• traumatic (e.g. tight “corn-row” braiding of hair, wearing tight pony tails, tight tying of turbans)

TELOGEN EFFLUVIUM
Clinical Presentation
• uniform decrease in hair density secondary to hairs leaving the growth (anagen) stage and entering the resting (telogen) stage of the cycle
Pathophysiology
• variety of precipitating factors
• hair loss typically occurs 2-4 mo after exposure to precipitant
• regrowth occurs within a few months but may not be complete

ANAGEN EFFLUVIUM
Clinical Presentation
• hair loss due to insult to hair follicle impairing its mitotic activity (growth stage)
Pathophysiology
• precipitated by chemotherapeutic agents (most common), other meds (bismuth, levodopa, colchicine, cyclosporine), exposure to chemicals (thallium, boron, arsenic)
• dose-dependent effect
• hair loss 7-14 d after single pulse of chemotherapy; most clinically apparent after 1-2 mo
• reversible effect; follicles resume normal mitotic activity few weeks after agent stopped

ALOPECIA AREATA
Clinical Presentation
• autoimmune disorder characterized by patches of complete hair loss often localized to scalp but can affect eyebrows, beard, eyelashes, etc.
• may be associated with dystrophic nail changes – fine stippling, pitting
• “exclamation mark” pattern (hairs fractured and have tapered shafts, i.e. looks like “!”)
• may be associated with pernicious anemia, vitiligo, thyroid disease, Addison’s disease
• spontaneous regrowth may occur within months of first attack (worse prognosis if young at age of onset and extensive loss)
• frequent recurrence often precipitated by emotional distress
Management
• generally unsatisfactory
• intralesional triamcinolone acetonide (corticosteroids) can be used for isolated patches
• UV or PUVA therapy
• immunomodulatory (diphencyprone)

Non-scarring alopecia: intact hair follicles on exam → biopsy not required (but may be helpful)
Scarring alopecia: absent hair follicles on exam → biopsy required

ALOPECIA AREATA Subtypes
• Alopecia totalis: loss of all scalp hair and eyebrows
• Alopecia universalis: loss of all body hair

DDx of Scarring (Cicatricial) Alopecia
Developmental/Hereditary Disorders
• Aplasia cutis congenita
• Epidermal nevi
• Romberg’s syndrome
• Generalized follicular hamartoma
Primary Causes
• Group 1: Lymphocytic
• DLE
• Lichen planopilaris
• Central centrifugal cicatricial alopecia
• Classic pseudopelade
• Group 2: Neutrophilic
• Folliculitis decalvans
• Dissecting scalp cellulitis
• Group 3: Mixed
• Acne keloidalis nuchae
Secondary Causes
• Infectious agents
• Bacterial (e.g. post-cellulitis)
• Fungal (e.g. tinea capitis)
• Neoplasms (e.g. BCC, SCC, lymphomas, and metastatic tumours)
• Physical agents
• Mechanical trauma
• Burns
• Radiotherapy
• Caustic chemicals

Scarring (Cicatricial) Alopecia
Clinical Presentation
• irreversible loss of hair follicles with fibrosis
Etiology
• physical: radiation, burns
• infections: fungal, bacterial, TB, leprosy, viral (HZV)
• inflammatory
  ▪ lichen planus (lichen planopilaris)
  ▪ DLE (note that SLE can cause an alopecia unrelated to DLE lesions which are non-scarring)
  ▪ morphea: “coup de sabre” with involvement of centre of scalp
  ▪ central centrifugal cicatricial alopecia: seen in up to 40% of black women, starting at central scalp, one of most commonly diagnosed scarring alopecias, may be associated with hair care practices in this population
Investigations
• biopsy from active border
Management
• infections: treat underlying infection
• inflammatory: topical/intralesional steroids, anti-inflammatory antibiotics, antimalarials

Precipitants of Telogen Effluvium
“SEND” hair follicles out of anagen and into telogen
Stress and Scalp disease (surgery)
Endocrine (hypothyroidism, post-partum)
Nutritional (iron and protein deficiency)
Drugs (citretin, heparin, lithium, IFN, β-blockers, valproic acid, SSRIs)
### Table 22. Nail Changes in Systemic and Dermatological Conditions

<table>
<thead>
<tr>
<th>Nail Abnormality</th>
<th>Definition/Etiology</th>
<th>Associated Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NAIL PLATE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clubbing</td>
<td>Proximal nail plate has greater than 180 degree angle to nail fold, watch-glass nails, bulbous digits</td>
<td>Cyanotic heart disease, bacterial endocarditis, pulmonary disorders, GI disorders, etc.</td>
</tr>
<tr>
<td>Koilonychia</td>
<td>Spoon shaped nails</td>
<td>Iron deficiency, malnutrition, DM</td>
</tr>
<tr>
<td>Onycholysis</td>
<td>Separation of nail plate from nail bed</td>
<td>Psoriasis, dermatophytes, thyroid disease</td>
</tr>
<tr>
<td>Onychogryphosis</td>
<td>Hypertrophy of the nail plate and subungal hyperkeratosis</td>
<td>Poor circulation, chronic inflammation, tinea</td>
</tr>
<tr>
<td>Onychohemia</td>
<td>Subungal hematoma</td>
<td>Trauma to nail bed</td>
</tr>
<tr>
<td>Onychomycosis</td>
<td>Fungal infection of nail (e.g. dermatophyte, yeast, mould)</td>
<td>HIV, DM, peripheral arterial disease</td>
</tr>
<tr>
<td>Onychocryptosis</td>
<td>Often hallux with congenital malalignment, painful inflammation, granulation tissue</td>
<td>Tight fitting shoes, excessive nail clipping</td>
</tr>
<tr>
<td><strong>SURFACE CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>V-shaped nicking</td>
<td>Distal margin has v-shaped loss of the nail plate</td>
<td>Darier’s disease (follicular dyskeratosis)</td>
</tr>
<tr>
<td>Pterygium inversus unguinum</td>
<td>Distal nail plate does not separate from underlying nail bed</td>
<td>Scleroderma</td>
</tr>
<tr>
<td>Pitting</td>
<td>Punctate depressions that migrate distally with growth</td>
<td>Psoriasis (random pattern), alopecia areata (geometric, gridshaped arrangement), eczema</td>
</tr>
<tr>
<td>Transverse ridging</td>
<td>Transverse depressions often more in central portion of nail plate</td>
<td>Serious acute illness slows nail growth (when present in all nails = Beau’s lines), eczema, chronic paronychia, trauma</td>
</tr>
<tr>
<td>Transverse white lines</td>
<td>Bands of white discolouration</td>
<td>Poisons, hypoalbuminemia (Muherke’s lines)</td>
</tr>
<tr>
<td><strong>COLOUR CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yellow</td>
<td></td>
<td>Tinea, jaundice, tetracycline, pityriasis rubra pilaris, yellow nail syndrome, psoriasis, tobacco use</td>
</tr>
<tr>
<td>Green</td>
<td></td>
<td>Pseudomonas</td>
</tr>
<tr>
<td>Black</td>
<td></td>
<td>Melanoma, hematoma</td>
</tr>
<tr>
<td>Brown</td>
<td></td>
<td>Nicotine use, psoriasis, poisons, longitudinal melanonychia (ethnic)</td>
</tr>
<tr>
<td>Splinter hemorrhages</td>
<td>Extravasation of blood from longitudinal vessels of nail bed, blood attaches to overlying nail plate and moves distally as it grows</td>
<td>Trauma, bacterial endocarditis, blood dyscrasias, psoriasis</td>
</tr>
<tr>
<td>Oil spots</td>
<td>Brown-yellow discolouration</td>
<td>Psoriasis</td>
</tr>
<tr>
<td><strong>NAIL FOLD CHANGES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpetic whitlow</td>
<td>HSV infection of distal phalanx</td>
<td>HSV infection</td>
</tr>
<tr>
<td>Paronychia</td>
<td>Local inflammation of the nail fold around the nail bed</td>
<td>Acute: painful infection Chronic: constant wetting (e.g. dishwashing, thumbsucking)</td>
</tr>
<tr>
<td>Nail fold telangiectasias</td>
<td></td>
<td>Scleroderma, SLE, dermatomyositis</td>
</tr>
<tr>
<td>Disease</td>
<td>Related Dermatoses</td>
<td></td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>AUTOIMMUNE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Painful apthous ulcers in oral cavity ± genital mucous membranes, erythema nodosum, acniform papules</td>
<td></td>
</tr>
<tr>
<td>Buerger’s disease</td>
<td>Superficial migratory thrombophlebitis, pallor, cyanosis, gangrene, ulcerations, digital resorptions</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Periorbital and extensor violaceous erythema, heliotrope with edema, Gottron’s papules (violaceous flat-topped papules with atrophy), periungual erythema, telangiectasia, calcinosis cutis</td>
<td></td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Subcutaneous nodules, stellate purpura, erythema, gangrene, splinter hemorrhages, livedo reticularis, ulceration</td>
<td></td>
</tr>
<tr>
<td>Reactive arthritis</td>
<td>Keratoderma blennorrhagica (on feet), balanitis circinata (on male penis)</td>
<td></td>
</tr>
<tr>
<td>Rheumatic fever</td>
<td>Petechiae, urticaria, erythema nodosum, rheumatic nodules, evanescent rash</td>
<td></td>
</tr>
<tr>
<td>Scleroderma</td>
<td>Raynaud’s, nonpitting edema, waxy/shiny/tense atrophic skin (morphea), ulcers, cutaneous calcification, periungual telangiectasia, acrosclerosis, salt-and-pepper pigmentation</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>Malar erythema, discoid rash (erythematous papules or plaques with keratotic scale, follicular plugging, atrophic scarring on face, hands, and arms), hemorrhagic bullae, palpable purpura, urticarial purpura, patchy/diffuse alopecia, mucosal ulcers, photosensitivity</td>
<td></td>
</tr>
<tr>
<td>Crohn’s disease/UC</td>
<td>Pyoderma gangrenosum, erythema nodosum, Sweet’s syndrome</td>
<td></td>
</tr>
<tr>
<td><strong>ENDOCRINE DISORDERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td>Generalized hyperpigmentation or limited to skin folds, buccal mucosa, and scars</td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td>Moon facies, purple striae, acne, hyperpigmentation, hirsutism, atrophic skin with telangiectasia</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>Infections (e.g. boils, carbuncles, Candidiasis, S. aureus, dermatophytoses, tinea pedis and cruris, infectious eczematoid dermatitis), pruritus, eruptive xanthomas, necrobiosis lipoidica diabeticum, granuloma annulare, diabetic foot, diabetic bullae, acanthosis nigricans, calciphylicasis</td>
<td></td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Moist, warm skin, seborrhea, acne, nail atrophy, hyperpigmentation, toxic alopecia, pretibial myxedema, acropachy, onycholyisis</td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Cool, dry, scaly, thickened, hyperpigmented skin; toxic alopecia with dry, coarse hair, brittle nails, myxedema, loss of lateral 1/3 eyebrows</td>
<td></td>
</tr>
<tr>
<td><strong>HIV-RELATED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>Viral (e.g. HSV, HZV, HPV, CMV, molluscum contagiosum, oral hairy leukoplakia), bacterial (impetigo, acniform folliculitis, dental caries, cellulitis, bacillary epitheloid angiomatosis, syphilis), fungal (candidiasis, histoplasmosis, cryptococcus, blastomycosis)</td>
<td></td>
</tr>
<tr>
<td>Inflammatory dermatoses</td>
<td>Seborrhea, psoriasis, pityriasis rosea, vasculitis</td>
<td></td>
</tr>
<tr>
<td>Malignancies</td>
<td>Kaposi’s sarcoma, lymphoma, BCC, SCC, MM</td>
<td></td>
</tr>
<tr>
<td><strong>MALIGNANCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Peutz-Jeghers: pigmented macules on lips/oral mucosa</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Paget’s disease: eroding scaling plaques of perineum</td>
<td></td>
</tr>
<tr>
<td>Cervix/anus/rectum</td>
<td>Paget’s disease: eczematous and crustig lesions of breast</td>
<td></td>
</tr>
<tr>
<td>Carcinoma</td>
<td>Paget’s disease: eczematous and crustig lesions of breast</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>Paget’s disease: eczematous and crustig lesions of breast</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Palmpplanter keratodema: thickened skin of palms/soles</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>Simple’s syndrome: multiple mucosal neumomas</td>
<td></td>
</tr>
<tr>
<td>Breast/ovary</td>
<td>Dermatomyositis: heliotrope erythema of eyelids and violaceous plaques over knuckles</td>
<td></td>
</tr>
<tr>
<td>Lymphoma/leukemia</td>
<td>Ataxia Telangiectasia: telangiectasia on pinna, bulb conjunctiva</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s Acute leukemia</td>
<td>Ichthyosis: generalized scaling especially on extremities, Sweet’s syndrome</td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bloom’s syndrome: butterfly erythema on face, Associated with short stature</td>
<td></td>
</tr>
<tr>
<td><strong>OTHERS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver disease</td>
<td>Pruritus, hyperpigmentation, spider nevi, palmar erythema, white nails (Terry’s nails), porphyria cutanea tarda, xanthomas, hair loss, jaundice</td>
<td></td>
</tr>
<tr>
<td>Renal disease</td>
<td>Pruritus, pigmentation, half and half nails, perforating dermatosis, calcificlaxis</td>
<td></td>
</tr>
<tr>
<td>Puritic urticaria papules and plaques of pregnancy</td>
<td>Erythematous papules or urticarial plaques in distribution of striae distensae: buttocks, thighs, upper inner arms and lower back</td>
<td></td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Pulpable purpura in cold-exposed areas, Raynaud’s, cold urticaria, acral hemorrhagic necrosis, bleeding disorders, associated with hepatitis C infection</td>
<td></td>
</tr>
</tbody>
</table>
Pediatric Exanthems

- see Pediatrics, P56

Miscellaneous Lesions

Angioedema and Urticaria

Angioedema
- deeper swelling of the skin involving subcutaneous tissues; often involves the eyes, lips, and tongue
- may or may not accompany urticaria
- hereditary or acquired forms
- hereditary angioedema (does not occur with urticaria)
  • onset in childhood; 80% have positive family history
  • recurrent attacks: 25% die from laryngeal edema
  • triggers: minor trauma, emotional upset, temperature changes
- types of acquired angioedema
  • acute allergic angioedema (allergens include food, drugs, contrast media, insect venom, latex)
  • non-allergic drug reaction (drugs include ACE inhibitors)
  • acquired C1 inhibitor deficiency
- treatment
  • prophylaxis with danazol or stanozolol for hereditary angioedema
  • epinephrine pen to temporize until patient reaches hospital in acute attack

Urticaria
- also known as "hives"
- transient, red, pruritic well-demarcated wheals
- each individual lesion lasts less than 24 h
- second most common type of drug reaction
- results from release of histamine from mast cells in dermis
- can also result after physical contact with allergen

<table>
<thead>
<tr>
<th>Table 24. Classification of Urticaria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Acute Urticaria</td>
</tr>
<tr>
<td>&gt;2/3 of cases</td>
</tr>
<tr>
<td>Attacks last &lt;6 wk</td>
</tr>
<tr>
<td>Individual lesions last &lt;24 h</td>
</tr>
<tr>
<td>Drugs: especially ASA, NSAIDs</td>
</tr>
<tr>
<td>Foods: nuts, shellfish, eggs, fruit</td>
</tr>
<tr>
<td>Idiopathic (vast majority)</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Insect stings (bees, wasps, hornets)</td>
</tr>
<tr>
<td>Percutaneous absorption: cosmetics, work exposures</td>
</tr>
<tr>
<td>Stress</td>
</tr>
<tr>
<td>Systemic diseases: SLE, endocrinopathy, neoplasm</td>
</tr>
<tr>
<td>Chronic Urticaria</td>
</tr>
<tr>
<td>&lt;1/3 of cases</td>
</tr>
<tr>
<td>Attacks last &gt;6 wk</td>
</tr>
<tr>
<td>Individual lesion lasts &lt;24 h</td>
</tr>
<tr>
<td>Idiopathic (90% of chronic urticaria patients)</td>
</tr>
<tr>
<td>Aeroallergens</td>
</tr>
<tr>
<td>Drugs (antibiotics, hormones, local anesthetics)</td>
</tr>
<tr>
<td>Foods and additives</td>
</tr>
<tr>
<td>Insect stings</td>
</tr>
<tr>
<td>Parasitic infections</td>
</tr>
<tr>
<td>Physical contact (animal saliva, plant resins, latex, metals, lotions, soap)</td>
</tr>
<tr>
<td>Direct mast cell release</td>
</tr>
<tr>
<td>Opiates, muscle relaxants, radio-contrast agents</td>
</tr>
<tr>
<td>Complement-mediated</td>
</tr>
<tr>
<td>Serum sickness, transfusion reactions</td>
</tr>
<tr>
<td>Infections, viral/bacterial (&gt;80% of urticaria in pediatric patients)</td>
</tr>
<tr>
<td>Urticarial vasculitis</td>
</tr>
<tr>
<td>Arachidonic acid metabolism</td>
</tr>
<tr>
<td>ASA, NSAIDs</td>
</tr>
<tr>
<td>Physical</td>
</tr>
<tr>
<td>Dermatographism (friction, rubbing skin), cold (ice cube, cold water), cholineric (hot shower, exercise), solar, pressure (shoulder strap, buttocks), aquagenic (exposure to water), adrenergic (stress), heat</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Mastocytosis, urticaria pigmentosa</td>
</tr>
</tbody>
</table>

Urticarial Vasculitis
- Individual lesions last >24 h
- Often painful, less likely pruritic; heals with bruise type lesions
- Requires biopsy

DDx for Urticaria
DAM HIVES
Drugs and foods
Allergic
Malignancy
Hereditary
Infection
Vasculitis
Emotions
Stings

Approach to Urticaria
- Thorough Hx and P/E
- Acute: no immediate investigations needed; consider referral for allergy testing
- Chronic: further investigations required: CBC and differential, urinalysis, ESR, TSH, LFTs to help identify underlying cause
- Vasculitic: biopsy of lesion and referral to dermatology

Wheat
- Typically erythematous flat-topped, palpable lesions varying in size with circumscribed dermal edema
- Individual lesion lasts <24 h
- Associated with mast cell release of histamine
- May be pruritic

Mastocytosis (Urticaria Pigmentosa)
Rare disease due to excessive infiltration of the skin by mast cells. It manifests as many reddish-brown elevated plaques and macules. Friction to a lesion produces a wheal surrounded by intense erythema (Darier’s sign), due to mast cell degranulation; this occurs within minutes
**Erythema Nodosum**

**Clinical Presentation**
- acute or chronic inflammation of subcutaneous fat (panniculitis)
- round, red, tender, poorly demarcated nodules
- sites: asymmetrically arranged on extensor lower legs, knees, arms, (typically shins)
- associated with arthralgia, fever, malaise

**Etiology**
- 40% are idiopathic
- drugs: sulfonamides, OCPs (also pregnancy), analgesics, trans retinoic acid
- infections: GAS, TB, histoplasmosis, Yersinia
- inflammation: sarcoidosis, Crohn’s > UC
- malignancy: acute leukemia, Hodgkin’s lymphoma

**Epidemiology**
- 15-30 yr old, F:M = 3:1
- lesions last for days and spontaneously resolve in 6 wk

**Investigations**
- chest x-ray (to rule out chest infection and sarcoidosis)
- throat culture, ASO titre, PPD skin test

**Management**
- symptomatic: bed rest, compressive bandages, wet dressings
- NSAIDs, intralesional steroids
- treat underlying cause

**Pruritus**

**Clinical Presentation**
- a sensation provoking a desire to scratch, with or without skin lesions
- lesions may arise from the underlying disease, or from excoriation causing crusts, lichenified plaques, or wheals

**Etiology**
- dermatologic – generalized
  - asthetic dermatitis (“winter itch” due to dry skin)
  - pruritus of senescent skin (may not have dry skin, any time of year)
  - infestations: scabies, lice
  - drug eruptions: ASA, antidepressants, opiates
  - psychogenic states
- dermatologic – local
  - atopic and contact dermatitis, lichen planus, urticaria, insect bites, dermatitis herpetiformis
  - infection: varicella, candidiasis
  - lichen simplex chronicus
  - prurigo nodularis
- systemic disease – usually generalized
  - hepatic: obstructive biliary disease, cholestatic liver disease of pregnancy
  - renal: chronic renal failure, uremia secondary to hemodialysis
  - hematologic: Hodgkin’s lymphoma, multiple myeloma, leukemia, polycythemia vera, hemochromatosis, Fe deficiency anemia, cutaneous T-cell lymphoma
  - neoplastic: lung, breast, gastric (internal solid tumours), non-Hodgkin’s lymphoma
  - endocrine: carcinoid, DM, hypothyroidism/hyperthyroidism
  - infectious: HIV, trichinosis, echinococcosis, hepatitis C
  - psychiatric: depression, psychosis
  - neurologic: post-herpetic neuralgia, multiple sclerosis

**Investigations**
- blood work: CBC, ESR, Cr/BUN, LFT, TSH, fasting blood sugar, stool culture and serology for parasites

**Management**
- treat underlying cause
- cool water compresses to relieve pruritus
- bath oil and emollient ointment (especially if xerosis is present)
- topical corticosteroid and antipruritics (e.g. menthol, camphor, phenol, mirtazapine, capsaicin)
- systemic antihistamines: H1 blockers are most effective, most useful for urticaria
- phototherapy with UVB or PUVA
- doxepin, amitriptyline
- immunosuppressive agents if severe: steroids and steroid sparing

**Wounds and Ulcers**
- see Plastic Surgery, PL8, PL15
Common Medications

Sunscreens and Preventative Therapy

Sunburn
- erythema 2-6 h post UV exposure often associated with edema, pain and blistering with subsequent desquamation of the dermis, and hyperpigmentation
- chronic UVA, UVB exposure leads to photoaging, immunosuppression, photocarcinogenesis
- prevention: avoid peak UVR (10 am-4 pm), wear appropriate clothing, wide-brimmed hat, sunglasses, and broad-spectrum sunscreen
- clothing with UV protection expressed as UV protection factor (UPF) is analogous to SPF of sunscreen

Sunscreens
- under ideal conditions an SPF of 10 means that a person who normally burns in 20 min will burn in 200 min following the application of the sunscreen
- topical chemical: absorbs UV light
  - requires application at least 15-60 min prior to exposure, should be reapplied every 2 h (more often if sweating, swimming)
  - UVB absorbers: PABA, salicylates, cinnamates, benzylidene camphor derivatives
  - UVA absorbers: benzophenones, anthranilates, dibenzoylmethanes, benzylidene camphor derivatives
- topical physical: reflects and scatters UV light
  - titanium dioxide, zinc oxide, kaolin, talc, ferric chloride, and melanin
  - all are effective against the UVA and UVB spectrum
  - less risk of sensitization than chemical sunscreens and waterproof, but may cause folliculitis or miliaria
- some sunscreen ingredients may cause contact or photocontact allergic reactions, but are uncommon

Management
- sunburn: if significant blistering present, consider treatment in hospital; otherwise, symptomatic treatment (cool wet compresses, oral anti-inflammatory, topical corticosteroids)
- antioxidants, both oral and topical are being studied for their abilities to protect the skin; topical agents are limited by their ability to penetrate the skin

Topical Steroids

Table 25. Potency Ranking of Topical Steroids

<table>
<thead>
<tr>
<th>Relative Potency</th>
<th>Relative Strength</th>
<th>Generic Names</th>
<th>Trade Names</th>
<th>Usage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weak</td>
<td>x1</td>
<td>hydrocortisone – 2.5%</td>
<td>Emo Cort®</td>
<td>Intertriginous areas, children, face, thin skin</td>
</tr>
<tr>
<td>Moderate</td>
<td>x3</td>
<td>hydrocortisone 17-valerate – 0.2% desonide mometasone furoate</td>
<td>Westcort® Tridesilon® Elocort®</td>
<td>Arm, leg, trunk</td>
</tr>
<tr>
<td>Potent</td>
<td>x6</td>
<td>betamethasone – 0.1% 17-valerate – 0.1% amcinonide</td>
<td>Betnovate® Celestoderm – V® Cyclocort®</td>
<td>Body</td>
</tr>
<tr>
<td>Very Potent</td>
<td>x9</td>
<td>betamethasone dipropionate – 0.05% fluocinonide – 0.05% halcinonide</td>
<td>Diprostone® Lidex, Topsyn gel® Lyderm® Halog®</td>
<td>Palms and soles</td>
</tr>
<tr>
<td>Extremely Potent</td>
<td>x12</td>
<td>clobetasol propionate – 0.05% betamethasone dipropionate ointment halobetasol propionate – 0.05%</td>
<td>Demovate® Diproline® Ultravate®</td>
<td>Palms and soles</td>
</tr>
</tbody>
</table>

Body Site: Relative Percutaneous Absorption

<table>
<thead>
<tr>
<th>Body Site</th>
<th>Relative Percutaneous Absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forearm</td>
<td>1.0</td>
</tr>
<tr>
<td>Plantar foot</td>
<td>0.14</td>
</tr>
<tr>
<td>Palm</td>
<td>0.83</td>
</tr>
<tr>
<td>Back</td>
<td>1.7</td>
</tr>
<tr>
<td>Scapula</td>
<td>3.7</td>
</tr>
<tr>
<td>Forehead</td>
<td>6.0</td>
</tr>
<tr>
<td>Cheeks</td>
<td>13.0</td>
</tr>
<tr>
<td>Scrotum</td>
<td>42.0</td>
</tr>
</tbody>
</table>

Calculation of strength of steroid compared to hydrocortisone on forearm: relative strength of steroid x relative percutaneous absorption

Surface Area

30 g covers full adult body once. Children have a greater surface area/volume ratio and there are consequently greater side effects

Side Effects of Topical Steroids
- Local: atrophy, perioral dermatitis, steroid acne, rosacea, contact dermatitis, tachyphylaxis (tolerance)
- Systemic: suppression of HPA axis

SPF = burn time with cream/burn time without cream
# Dermatologic Therapies

## Table 26. Common Topical Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcipotriol (Dovonex®)</td>
<td>0.005% cream, ointment, scalp solution, apply bid For maintenance therapy apply OD</td>
<td>Psoriasis</td>
<td>Burning, itching, skin irritation, worsening of psoriasis Avoid face, mucous membranes, eyes; wash hands after application Maximum weekly dosage of cream by age: 2-5 yr – 25 g/wk 6-10 yr – 50 g/wk 11-14 yr – 75 g/wk &gt;14 yr – 100 g/wk Inactivated by light (do not apply before phototherapy)</td>
</tr>
<tr>
<td>Imiquimod (Aldara®)</td>
<td>5% cream applied 3x/wk Apply at bedtime, leave on 6-10 h, then wash off with mild soap and water Max duration 16 wk</td>
<td>Genital warts Cutaneous warts AK Superficial BCC</td>
<td>Avoid natural/artificial sun exposure Local skin and application site reactions Erythema, ulceration, edema, flu-like symptoms Low toxicity, excellent results Works best for warts on mucosal surfaces May induce inflammation and erosion</td>
</tr>
<tr>
<td>Permethrin (Kwellada® P Lotion and Nix® Dermal Cream)</td>
<td>5% cream, applied once overnight to all skin areas from neck down, repeated one week later</td>
<td>Scabies (Kwellada-P Lotion, Nix® Dermal Cream) Pediculosis (Kwellada-P Crème Rinse®, Nix Crème Rinse®)</td>
<td>Do not use in children &lt;2 yr Hypersensitivity to drug, or known sensitivity to chrysanthemums Local reactions only (resolve rapidly); including burning, pruritus Low toxicity, excellent results Consider second application after 7 d</td>
</tr>
<tr>
<td>Pimecrolimus (Elidel®)</td>
<td>1.0% cream bid Use for as long as lesions persist and discontinue upon resolution of symptoms</td>
<td>AD (mild to moderate)</td>
<td>Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expense</td>
</tr>
<tr>
<td>Tacrolimus Topical (Protopic®)</td>
<td>0.03% (children) or 0.1% (adults) ointment bid Continue for duration of disease PLUS 1 wk after clearing</td>
<td>AD (mild to moderate)</td>
<td>Burning Lacks adverse effects of steroids May be used on all skin surfaces including head, neck, and intertriginous areas Expense</td>
</tr>
</tbody>
</table>

## Table 27. Common Oral Therapies

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acitretin (Soriatane®)</td>
<td>25-50 mg PO OD; maximum 75 mg/d</td>
<td>Severe psoriasis</td>
<td>Monitoring strategies Monitor lipids, LFTs at baseline and q1-2wk until stable Contraindications Women of childbearing potential unless strict contraceptive requirements are met Drug interactions Other systemic retinoids, methotrexate, tetracyclines, certain contraceptives May be combined with PUVA phototherapy (known as re-PUVA)</td>
</tr>
<tr>
<td>Antivirals</td>
<td>famcyclovir (Famvir®) 250 mg PO tid x 7-10 d (for 1st episode of genital herpes) 125 mg PO bid x 5 d (for recurrent genital herpes)</td>
<td>Chickenpox Herpes zoster Genital herpes Acute and prophylactic to reduce transmission in infected patients Herpes labialis</td>
<td>Side effects Headache, nausea, diarrhea, abdominal pain Reduce dose if impaired renal function</td>
</tr>
<tr>
<td>Cyclosporin (Neoral®)</td>
<td>2-4 mg/kg/d PO divided bid Max 4 mg/kg/d After 4 wk may increase by 0.5 mg/kg/d q2wks Concomitant dose of magnesium may protect the kidneys</td>
<td>Psoriasis May also be effective in: Lichen planus EM Recalcitrant urticaria Recalcitrant AD</td>
<td>Monitoring strategies Blood pressure, renal function Contraindications Abnormal renal function, uncontrolled hypertension, malignancy (except NMSC), uncontrolled infection, immunodeficiency (excluding autoimmune disease), hypersensitivity to drug Long-term effects preclude use of cyclosporin for &gt;2 yr; discontinue earlier if possible May consider rotating therapy with other drugs to minimize adverse effects of each drug</td>
</tr>
<tr>
<td>Drug Name</td>
<td>Dosing Schedule</td>
<td>Indications</td>
<td>Comments</td>
</tr>
<tr>
<td>-----------</td>
<td>-----------------</td>
<td>-------------</td>
<td>----------</td>
</tr>
<tr>
<td><strong>Dapsone</strong></td>
<td>50-100-150 mg PO OD tapering to 25-50 mg PO OD to as low as 50 mg 2x/wk</td>
<td>Dermatitis herpetiformis, neutrophilic dermatoses</td>
<td>Monitoring strategies: Obtain G6PD levels before initiating; in the initial two wk obtain methemoglobin levels and follow blood counts carefully for the first few months. Side effects include Neuropathy, Hemolysis (Vitamin C and E supplementation can help prevent this). Drug interactions include Substrate of CYP2C8/9 (minor), 2C19 (minor), 2E1 (minor), 3A4 (major). Often a dramatic response within hours. Monitoring strategies: Obtain G6PD levels before initiating; in the initial two wk obtain methemoglobin levels and follow the blood counts carefully for the first few months.</td>
</tr>
<tr>
<td><strong>Isotretinoin</strong> (Accutane®)</td>
<td>0.5-1 mg/kg/d given OD, to achieve a total dose of 120 mg/kg (20-24 wk)</td>
<td>Severe nodular and/or inflammatory acne Acne conglobata Recalcitrant acne Widespread comedonal acne</td>
<td>Monitoring strategies: Baseline lipid profile and LFTs before treatment, β-hCG. Contraindications: Teratogenic – in sexually active females, 2 forms of reliable contraception necessary. Generally regarded as unsafe in lactation. Side effects: Night blindness, decreased tolerance to contact lenses, dry mucous membranes. May transiently exacerbate acne, dry skin. Depression, myalgia. Drug interactions: Do not use at the same time as tetracycline or minocycline – both may cause pseudotumour cerebri. Discontinue vitamin A supplements. Drug may be discontinued at 16-20 wk when nodule count has dropped by &gt;70%; a second course may be initiated after 2 mo prn. Refractory cases may require &gt;3 courses.</td>
</tr>
<tr>
<td><strong>Itraconazole</strong> (Sporanox®)</td>
<td>100-400 mg PO OD, depending on infection treated: Tinea corporis/cruris: 200 mg PO OD x 7 d Tinea pedis: 200 mg PO bid x 7 d Tinea versicolor: 200 mg PO OD x 7 d Toenails with or without fingernail involvement: 200 mg PO bid x 7 d once per month, repeated 3x. Fingernail involvement only: 200 mg bid PO x 7 d once per month, repeated 2x</td>
<td>Onychomycosis Tinea corporis, cruris, pedis, versicolor, capitis</td>
<td>Contraindications: CHF. Side effects: Serious hepatotoxicity. Drug Interactions: Inhibits CYP3A4. Increases concentration of some drugs metabolized by this enzyme (i.e. statins, diabetic drugs). Give capsules with food; capsules must be swallowed whole.</td>
</tr>
<tr>
<td><strong>Ivermectin</strong> (Mectizan®, Stromectol®)</td>
<td>200-250 µg/kg PO qweekly x 2 take once as directed; repeat one week later</td>
<td>Onchocerciasis (USA only). Not licensed for use in Canada. Also effective for: scabies.</td>
<td>No significant serious side effects. Efficacious.</td>
</tr>
<tr>
<td><strong>Methotrexate</strong> (Trexall®)</td>
<td>10-20 mg qwk, PO, IM, or IV Max: 30 mg/wk. To minimize side effects, administer with folic acid supplementation: 1-5 mg OD</td>
<td>Psoriasis AD Lymphomatoid papulosis May also be effective in: cutaneous sarcoidosis</td>
<td>Monitoring strategies: Baseline renal, liver, and hematological studies. Contraindications: Pregnancy, lactation, alcohol abuse, liver dysfunction, immunodeficiency syndrome, blood dyscrasias, hypersensitivity to drug. Restricted to severe, recalcitrant or disabling psoriasis not adequately responsive to other forms of therapy. May be combined with cyclosporine to allow lower doses of both drugs.</td>
</tr>
<tr>
<td><strong>Minocycline</strong> (Minocin®)</td>
<td>50-100 mg PO bid Taper to 50 mg PO OD as acne lessens</td>
<td>Acne vulgaris Rosacea</td>
<td>Contraindications: Caution if impaired renal or liver function. Drug interactions: Do not use with isotretinoin (Accutane®). Side effects: Extensive; affects multiple organ systems including CNS, teeth, eyes, bones, renal, and skin (photosensitivity and blue pigmentation). Drug-induced lupus (check p-ANCA). Alternative to tetracycline.</td>
</tr>
<tr>
<td><strong>OCPs</strong></td>
<td>TriCyclen Diane 35 Alesse</td>
<td>Hormonal acne (chin, jawline). Acne associated with polycystic ovarian syndrome or other endocrine abnormalities</td>
<td>Contraindications: Smoking, HIV, migraine with aura, pregnancy. Routine gynecological health maintenance should be up to date.</td>
</tr>
<tr>
<td><strong>Spironolactone</strong></td>
<td>50-100 mg PO OD alone or with OCPs</td>
<td>Hormonal acne (chin, jawline). Acne with endocrine abnormality</td>
<td>Contraindications: Menstrual irregularities at higher doses if not on OCPs. Breast tenderness, mild diuresis common. Risk of hyperkalemia – counsel patients to reduce intake of potassium rich foods such as bananas.</td>
</tr>
</tbody>
</table>
### Table 27. Common Oral Therapies (continued)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Terbinafine**  
(Lamisil®) | 250 mg PO OD x 2 wk  
Fingernails x 6 wk  
Toenails x 12 wk  
Confirm diagnosis prior to treatment | Onychomycosis  
Tinea corporis, cruris, pedis, capitis | Contraindications:  
Pregnancy, chronic or active liver disease  
Drug interactions:  
Potent inhibitor of CYP2D6; use with caution when also taking  
`-blockers, certain anti-arrhythmic agents, MAOI type B, and/or  
antipsychotics  
Drug concentrates rapidly in skin, hair, and nails at levels associated with fungicidal activity |
| **Tetracycline** | 250-500 mg PO bid to tid  
Taken 1 h before or 2 h after a meal | Acne vulgaris  
Rosacea  
Bullous pemphigoid | Contraindications:  
Severe renal or hepatic dysfunction |

### References


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White JD, Gretchkin JM. The rational clinical examination. Does this patient have a mole or a melanoma? JAMA 1999;280:696-701.


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## Initial Patient Assessment/Management

### 1. Rapid Primary Survey

- Airway maintenance with C-spine control
- Breathing and ventilation
- Circulation (pulses, hemorrhage control)
- Disability (neurological status)
- Exposure (complete) and Environment (temperature control)
- Continually reassessed during secondary survey
- **IMPORTANT**: Always watch for signs of shock while doing primary survey

#### A. AIRWAY

- First priority is to secure airway
- Assume a cervical injury in every trauma patient and immobilize with collar
- Assess ability to breathe and speak
- Can change rapidly, therefore reassess frequently
- Assess for facial fractures/edema/burns (impending airway collapse)

#### Airway Management

- Permit adequate oxygenation and ventilation

#### 1. Basic Airway Management

- Protect the C-spine
- Head-tilt (if C-spine injury not suspected) or jaw thrust to open the airway
- Sweep and suction to clear mouth of foreign material

#### 2. Temporizing Measures

- Nasopharyngeal airway (if gag reflex present, i.e. conscious)
- Oropharyngeal airway (if gag reflex absent, i.e. unconscious)
- “Rescue” airway devices (e.g. laryngeal mask airway, Combitube®)
- Transtracheal jet ventilation through cricothyroid membrane (last resort)

#### 3. Definitive Airway Management

- ETT intubation with in-line stabilization of C-spine
  - Oropharyngeal ± RSI preferred
  - Nasotracheal may be better tolerated in conscious patient
  - Relatively contraindicated with basal skull fracture
  - Does not provide 100% protection against aspiration
  - Surgical airway (if unable to intubate using oral/nasal route and unable to ventilate)
  - Cricothyroidotomy

**Contraindications to Intubation**

- Supraglottic/glottic pathology that would preclude successful intubation

---

### Approach to the Critically Ill Patient

1. Rapid Primary Survey (RPS)
2. Resuscitation (often concurrent with RPS)
3. Detailed Secondary Survey
4. Definitive Care

### Signs of Airway Obstruction

- Agitation, confusion, “universal choking sign”
- Respiratory distress
- Failure to speak, dysphonia
- Cyanosis

### Medications that can be Delivered via ETT

- Naloxone (Narcan®)
- Atropine
- Ventolin® (salmeterol)
- Epinephrine
- Lidocaine

---
**B. BREATHING**

- **Look**
  - mental status (anxiety, agitation, decreased LOC), colour, chest movement (bilateral vs. asymmetrical), respiratory rate/effort, nasal flaring
- **Listen**
  - auscultate for signs of obstruction (e.g. stridor), breath sounds, symmetry of air entry, air escaping
- **Feel**
  - tracheal shift, chest wall for crepitus, flail segments, sucking chest wounds, subcutaneous emphysema

**Breathing Assessment**
- objective measures of respiratory function: rate, oximetry, ABG, A-a gradient

**Management of Breathing**
- nasal prongs → simple face mask → non-rebreather mask → CPAP/BiPAP (in order of increasing FiO2)
- Venturi mask: used to precisely control O2 delivery
- Bag-Valve mask and CPAP to supplement inadequate ventilation

**C. CIRCULATION**

**Definition of Shock**
- inadequate organ and tissue perfusion with oxygenated blood (brain, kidney, extremities)

**Table 1. Major Types of Shock**

<table>
<thead>
<tr>
<th>Type</th>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Distributive</th>
<th>Obstructive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage (external and internal)</td>
<td>Hemorrhage (external and internal)</td>
<td>Myocardial ischemia</td>
<td>Septic</td>
<td>Cardiac tamponade</td>
</tr>
<tr>
<td>Severe burns</td>
<td>Myocardial ischemia</td>
<td>Septic</td>
<td>Cardiac tamponade</td>
<td></td>
</tr>
<tr>
<td>High output fistulas</td>
<td>Dyshytrainingia</td>
<td>Anaphylactic</td>
<td>Obstructive (vasodilation)</td>
<td>Tension pneumothorax</td>
</tr>
<tr>
<td>Dehydration (diarrhea, DKA)</td>
<td>CHF</td>
<td>Neurogenic (spinal cord injury)</td>
<td>Cardiac valve problems</td>
<td>PE</td>
</tr>
<tr>
<td></td>
<td>Cardiomyopathies</td>
<td>Constrictive pericarditis</td>
<td>Cardiac valve problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cardiac valve problems</td>
<td>Cardiac valve problems</td>
<td>Cardiac valve problems</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical Evaluation**
- early: tachypnea, tachycardia, narrow pulse pressure, reduced capillary refill, cool extremities, and reduced central venous pressure
- late: hypotension and altered mental status, reduced urine output

**Table 2. Estimation of Degree of Hemorrhagic Shock**

<table>
<thead>
<tr>
<th>Class</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood loss</td>
<td>&lt;750 cc</td>
<td>750-1,500 cc</td>
<td>1,500-2,000 cc</td>
<td>&gt;2,000 cc</td>
</tr>
<tr>
<td>% of blood volume</td>
<td>&lt;15%</td>
<td>15-30%</td>
<td>30-40%</td>
<td>&gt;40%</td>
</tr>
<tr>
<td>Pulse</td>
<td>&lt;100</td>
<td>&gt;100</td>
<td>&gt;120</td>
<td>&gt;140</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Normal</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>20</td>
<td>30</td>
<td>35</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Capillary refill</td>
<td>Normal</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Urinary output</td>
<td>30 cc/h</td>
<td>20 cc/h</td>
<td>10 cc/h</td>
<td>None</td>
</tr>
<tr>
<td>Fluid replacement</td>
<td>Crystalloid</td>
<td>Crystalloid</td>
<td>Crystalloid + blood</td>
<td>Crystalloid + blood</td>
</tr>
</tbody>
</table>

**Indications for Intubation**
- Unable to protect airway (e.g. GCS <8; airway trauma)
- Inadequate oxygenation with spontaneous respiration (O2 saturation <96% with 100% O2, or rising pCO2)
- Profound shock
- Anticipatory: in trauma, overdose, CHF, asthma, COPD, and smoke inhalation injury
- Anticipated transfer of critically ill patients

**Rescue Techniques in Intubation**
- Bougie (used like a guidewire)
- Glidescope®
- Lighted stylet (use light through skin to determine if ETT in correct place)
- Fiberoptic intubation – indirect visualization using fiberoptic cable

**Noisy breathing is obstructed breathing until proven otherwise**

**Shock in a trauma patient is hemorrhagic until proven otherwise**

**Causes of Shock**
- Septic, spinal/neurogenic, Hemorrhagic
- Obstetric (e.g. tension pneumothorax, cardiac tamponade, PE)
- Cardiogenic (e.g. blunt myocardial injury, dysrhythmia, MI)
- Anaphylactic
- Endocrine (e.g. Addison’s, myxedema, coma)
- Drugs

**Estimated Systolic Blood Pressure Based on Position of Most Distal Palpable Pulse**

<table>
<thead>
<tr>
<th>sBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radial</td>
</tr>
<tr>
<td>Femoral</td>
</tr>
<tr>
<td>Carotid</td>
</tr>
</tbody>
</table>
Management of Hemorrhagic Shock
- clear airway and breathing either first or simultaneously
- apply direct pressure on external wounds while elevating extremities. Do not remove impaled objects in the emergency room setting as they may tamponade bleeds
- start TWO LARGE BORE (14-16G) IVs in the brachial/cephalic vein of each arm
- run 1-2 L bolus of IV Normal Saline/Ringer’s Lactate (warmed, if possible)
- if continual bleeding or no response to crystalloids, consider pRBC transfusion, ideally crossmatched. If crossmatched blood is unavailable, consider O- for women of childbearing age and O+ for men. Use FFP, platelets or tranexamic acid in early bleeding
- consider common sites of internal bleeding (abdomen, chest, pelvis, long bones) where surgical intervention may be necessary

D. DISABILITY
- assess LOC using GCS
  - pupils
    - assess equality, size, symmetry, reactivity to light
    - inequality/sluggish suggests local eye problem or lateralizing CNS lesion
    - relative afferent pupillary defect (swinging light test) – optic nerve damage
  - extraocular movements and nystagmus
  - fundoscopy (papilledema, hemorrhages)
  - reactive pupils + decreased LOC → metabolic or structural cause
  - non-reactive pupils + decreased LOC → structural cause (especially if asymmetric)
- Glasgow Coma Scale
  - for use in trauma patients with decreased LOC; good indicator of severity of injury and neurosurgical prognosis
  - most useful if repeated; change in GCS with time is more relevant than the absolute number
  - less meaningful for metabolic coma
  - patient with deteriorating GCS needs immediate attention
  - prognosis based on best post-resuscitation GCS
  - reported as a 3 part score: Eyes + Verbal + Motor = Total
  - if patient intubated, GCS score reported out of 10 + T (T = tubed, i.e. no verbal component)

Table 3. Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eyes Open</th>
<th>Best Verbal Response</th>
<th>Best Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneously</td>
<td>Answers questions appropriately 5</td>
<td>Obey's commands 6</td>
</tr>
<tr>
<td>To voice</td>
<td>Confused, disoriented 4</td>
<td>Localizes to pain 5</td>
</tr>
<tr>
<td>To pain</td>
<td>Inappropriate words 3</td>
<td>Withdraws from pain 4</td>
</tr>
<tr>
<td>No response</td>
<td>Incomprehensible sounds 2</td>
<td>Decorticate (flexion) 3</td>
</tr>
<tr>
<td></td>
<td>No verbal response 1</td>
<td>Decerebrate (extension) 2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No response 1</td>
</tr>
</tbody>
</table>

13-15 = mild injury, 9-12 = moderate injury, ≤8 = severe injury
See Table 36, ER57 for modified GCS for infants and children

E. EXPOSURE/ENVIRONMENT
- undress patient completely and assess entire body for injury; log roll to examine back
- DRE
- keep patient warm with a blanket ± radiant heaters; avoid hypothermia
- warm IV fluids/blood
- keep providers safe (contamination, combative patient)

2. Resuscitation
- done concurrently with primary survey
- attend to ABCs
- manage life-threatening problems as they are identified
  - vital signs q5-15 min
  - ECG, BP, and O2 monitors
- Foley catheter and NG tube if indicated
- tests and investigations: CBC, electrolytes, BUN, Cr, glucose, amylase, INR/PTT, β-hCG, toxicology screen, cross and type

Fluid Resuscitation
- Give bolus until HR decreases, urine output increases, and patient stabilizes
- Maintenance: 4:2:1 rule
  - 0-10 kg: 4 cc/kg/h
  - 10-20 kg: 2 cc/kg/h
  - Remaining weight: 1 cc/kg/h
- Replace ongoing losses and deficits (assume 10% of body weight)

3:1 Rule
Since only 30% of infused isotonic crystalloids remains in intravascular space, you must give 3x estimated blood loss

Unilateral, Dilated, Non-Reactive Pupil, Think
- Focal mass lesion
- Epidural hematoma
- Subdural hematoma

Contraindications to Foley Insertion
- Blood at urethral meatus
- Scrotal hematoma
- High-riding prostate on DRE

NG Tube Contraindications
- Significant mid-face trauma
- Basal skull fracture
Table 4. 2010 AHA CPR Guidelines

<table>
<thead>
<tr>
<th>Step/Action</th>
<th>Adult: &gt;8 yr</th>
<th>Child: 1-8 yr</th>
<th>Infant: &lt;1 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway</td>
<td>Head tilt-chin lift</td>
<td>Abdominal thrust</td>
<td>Back slaps and chest thrusts</td>
</tr>
<tr>
<td>Breaths</td>
<td>2 breaths at 1 second/breath – stop once see chest rise</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign-Body Airway Obstruction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compressions</td>
<td>In the centre of the chest, between nipples</td>
<td>Just below nipple line</td>
<td></td>
</tr>
<tr>
<td>Compression landmarks</td>
<td>2 hands: heel of 1 hand with second hand on top</td>
<td>2 hands: heel of 1 hand with second hand on top, or 1 hand: heel of 1 hand only</td>
<td>2 fingers, or thumbs</td>
</tr>
<tr>
<td>Compression depth</td>
<td>At least 2 inches</td>
<td>About ( \frac{1}{3} ) to ( \frac{1}{2} ) the depth of the chest</td>
<td></td>
</tr>
<tr>
<td>Compression rate</td>
<td>100/min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compression-ventilation ratio</td>
<td></td>
<td>30 compressions to 2 ventilations</td>
<td></td>
</tr>
<tr>
<td>Compression-only CPR</td>
<td>Hands-only CPR is preferred if the bystander is not trained or does not feel confident in their ability to provide conventional CPR or if the bystander is trained but chooses to use compressions only</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Defibrillation</td>
<td>Immediate defibrillation for all rescuers responding to a sudden witnessed collapse</td>
<td>Compressions (5 cycles/2 min) before AED is considered if unwitnessed arrest</td>
<td></td>
</tr>
<tr>
<td>Manual defibrillators are preferred for children and infants but can use adult dose AED if a manual defibrillator is not available</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3. Secondary Survey

- done after rapid primary survey problems have been addressed
- identifies major injuries or areas of concern
- full physical exam and x-rays (C-spine, chest, pelvis – required in blunt trauma, consider T-spine and L-spine)

HISTORY

- “SAMPLE”: Signs and symptoms, Allergies, Medications, Past medical history, Last meal, Events related to injury

![FAST view: Normal vs Free Fluid](image-url)

**Figure 2. Four areas of a FAST**
PHYSICAL EXAM

Head and Neck
• palpation of facial bones, scalp

Chest
• inspect for: 1. midline trachea and 2. flail segment: ≥2 rib fractures in ≥2 places; if present look for associated hemothorax, pneumothorax, and contusions
• auscultate lung fields
• palpate for subcutaneous emphysema

Abdomen
• assess for peritonitis, abdominal distention, and evidence of intra-abdominal bleeding
• DRE for GI bleed, high riding prostate and anal tone

Musculoskeletal
• examine all extremities for swelling, deformity, contusions, tenderness, ROM
• check for pulses (using Doppler probe) and sensation in all injured limbs
• log roll and palpate thoracic and lumbar spines
• palpate iliac crests and pubic symphysis and assess pelvic stability (lateral, AP, vertical)

Neurological
• GCS
• full cranial nerve exam
• alterations of rate and rhythm of breathing are signs of structural or metabolic abnormalities with progressive deterioration in breathing indicating a failing CNS
• assess spinal cord integrity
• conscious patient: assess distal sensation and motor function
• unconscious patient: response to painful or noxious stimulus applied to extremities

INITIAL IMAGING
• non-contrast CT head/face/C-spine (rule out fractures and bleeds)
• chest x-ray
• FAST (see Figure 2) or CT abdomen/pelvis (if stable)
• pelvis x-ray

Ethical Considerations

Consent to Treatment: Adults
• see Ethical, Legal, and Organizational Medicine, ELOAM7
• Emergency Rule: consent is not needed when a patient is at imminent risk from a serious injury AND obtaining consent is either: a) not possible, OR b) would increase risk to the patient
  • assumes that most people would want to be saved in an emergency
• any capable and informed patient can refuse treatment or part of treatment, even if it is life-saving
• exceptions to the Emergency Rule - treatment cannot be initiated if
  • a competent patient has previously refused the same or similar treatment and there is no evidence to suggest the patient’s wishes have changed
  • an advanced directive is available (e.g. do not resuscitate order)
  • NOTE: refusal of help in a suicide situation is NOT an exception; care must be given
  • if in doubt, initiate treatment
• care can be withdrawn if necessary at a later time or if wishes are clarified by family

Consent to Treatment: Children
• treat immediately if patient is at imminent risk
• parents/guardians have the right to make treatment decisions
• if parents refuse treatment that is life-saving or will potentially alter the child’s quality of life, CAS must be contacted – consent of CAS is needed to treat

Other Issues of Consent
• need consent for HIV testing, as well as for administration of blood products
• however, if delay in substitute consent for blood transfusions puts patient at risk, transfusions can be given

Duty to Report
• law may vary depending on province and/or state
• examples: gunshot wounds, potential drunk drivers, suspected child abuse, various communicable diseases, medical unsuitability to drive, risk of substantial harm to others
## Traumatology

- epidemiology
  - leading cause of death in patients <45 yr
  - 4th highest cause of death in North America
  - causes more deaths in children/adolescents than all diseases combined
- trimodal distribution of death
  - minutes: lethal injuries, death usually at the scene
  - early: death within 4-6 h – “golden hour” (decreased mortality with trauma care)
  - days-weeks: death from multiple organ dysfunction, sepsis, etc.
- injuries fall into two categories
  - blunt (most common): MVC, pedestrian-automobile impact, motorcycle collision, fall, assault, sports
  - penetrating (increasing in incidence): gunshot wound, stabbing, impalement

### Considerations for Traumatic Injury

- important to know the mechanism of injury in order to anticipate traumatic injuries
- always look for an underlying cause (alcohol, medications, illicit substances, seizure, suicide attempt, medical problem)
- always inquire about HI, loss of consciousness, amnesia, vomiting, headache, and seizure activity

<table>
<thead>
<tr>
<th>Table 5. Mechanisms and Considerations of Traumatic Injuries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanism of Injury</td>
</tr>
<tr>
<td>MVC</td>
</tr>
<tr>
<td>Pedestrian-Automobile Impact</td>
</tr>
<tr>
<td>Falls</td>
</tr>
</tbody>
</table>

## Head Trauma

- see Neurosurgery, NS29
- 60% of MVC-related deaths are due to HI

### Specific Injuries

- fractures
  - Dx: non-contrast head CT and physical exam
  - A. skull fractures
    - vault fractures
      - linear, non-depressed
        - most common
        - typically occur over temporal bone, in area of middle meningeal artery (commonest cause of epidural hematoma)
      - depressed
        - open (associated overlying scalp laceration and torn dura, skull fracture disrupting paranasal sinuses or middle ear) vs. closed
    - basal skull
      - typically occur through floor of anterior cranial fossa (longitudinal more common than transverse)
      - clinical diagnosis superior as poorly visualized on CT
  - B. facial fractures (see Plastic Surgery, PS29)
    - neuronal injury
    - beware of open fracture or sinus fractures (risk of infection)
    - severe facial fractures may pose risk to airway from profuse bleeding

- High Risk Injuries
  - MVC at high speed, resulting in ejection from vehicle
  - Motorcycle collisions
  - Vehicle vs. pedestrian crashes
  - Fall from height ≥12 ft (3.6 m)

### Signs of Basal Skull Fracture

- Battle’s sign (bruised mastoid process)
- Hemotympanum
- Raccoon eyes (periorbital bruising)
- CSF rhinorrhea/otorrhea
scalp laceration
- can be a source of significant bleeding
- achieve hemostasis, inspect and palpate for skull bone defects ± CT head (rule-out skull fracture)

neuronal injury
A. diffuse
- mild TBI = concussion
  - transient alteration in mental status that may involve loss of consciousness
    - hallmarks of concussion: confusion and amnesia, which may occur immediately after the trauma or minutes later
    - loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h
- diffuse axonal injury
  - mild: coma 6-24 h, possibly lasting deficit
  - moderate: coma >24 h, little or no signs of brainstem dysfunction
  - severe: coma >24 h, frequent signs of brainstem dysfunction

B. focal injuries
- contusions
- intracranial hemorrhage (epidural, subdural, intracerebral)

ASSESSMENT OF BRAIN INJURY

History
- pre-hospital status
- mechanism of injury

Physical Exam
- assume C-spine injury until ruled out
- vital signs
  - shock (not likely due to isolated brain injury, except in infants)
  - Cushing's response to increasing ICP (bradycardia, HTN, irregular respirations)
- severity of injury determined by
  1. LOC
    - GCS ≤8 intubate, any change in score of 3 or more = serious injury
    - mild TBI = 13-15, moderate = 9-12, severe = 3-8
  2. pupils: size, anisocoria >1 mm (in patient with altered LOC), response to light
  3. lateralizing signs (motor/sensory)
    - may become more subtle with increasing severity of injury
- reassess frequently

Investigations
- labs: CBC, electrolytes, PT/PTT or INR/PTT, glucose, toxicology screen
- CT scan (non-contrast) to exclude intracranial hemorrhage/hematoma
- C-spine imaging, often with CT head and neck to exclude intracranial hemorrhage/hematoma

Management
- goal in ED: reduce secondary injury by avoiding hypoxia, ischemia, decreased CPP, seizure
- ABCs
  - ensure oxygen delivery to brain through intubation and prevent hypercarbia
  - maintain BP (sBP >90)
  - treat other injuries
- early neurosurgical consultation for acute and subsequent patient management
- medical management
  - seizure treatment/prophylaxis
    - benzodiazepines, phenytoin, phenobarbital
    - steroids are of no proven value
  - treat suspected raised ICP → consider if HI with signs of increased ICP:
    - intubate
    - calm (sedate) if risk for high airway pressures or agitation
    - paralyze if agitated
    - hyperventilate (100% O2) to a pCO2 of 30-35 mmHg
    - elevate head of bed to 20º
    - adequate BP to ensure good cerebral perfusion
    - diurese with mannitol 1g/kg infused rapidly (contraindicated in shock/renal failure)

Disposition
- neurological ICU admission for severe HI
- in hemodynamically unstable patient with other injuries, prioritize most life-threatening injuries and maintain cerebral perfusion
- for minor HI not requiring admission, provide 24 h HI protocol to competent caregiver, follow-up with neurology as even seemingly minor HI may cause lasting deficits
Mild Traumatic Brain Injury

Epidemiology
- TBI results in 1.7 million deaths, hospitalizations, and ED visits each year (US)
- 75% are estimated to be mild TBI; remainder are moderate or severe (see Neurosurgery, NS31)
- highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features
- somatic: headache, sleep disturbance, N/V, blurred vision
- cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
- emotion and behaviour: impulsivity, irritability, depression
- severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils

Etiology
- falls, MVC, struck by an object, assault, sports

Investigations
- neurological exam
- concussion recognition tool (see thinkfirst.ca)
- imaging – CT as per Canadian CT Head Rules, or MRI if worsening symptoms despite normal CT

Treatment
- close observation and follow-up; for patients at risk of intracranial complications, give appropriate discharge instructions to patient and family; watch for changes to clinical features above, and if change, return to ED
- hospitalization with normal CT (GCS <15, seizures, bleeding diastasis), or with abnormal CT
- early rehabilitation to maximize outcomes
- pharmacological management of pain, depression, headache
- follow Return to Play guidelines

Prognosis
- most recover with minimal treatment
- athletes with previous concussion are at increased risk of cumulative brain injury
- repeat TBI can lead to life-threatening cerebral edema or permanent impairment

Spine and Spinal Cord Trauma

- assume cord injury with significant falls (>12 ft), deceleration injuries, blunt trauma to head, neck, or back
- spinal immobilization (cervical collar, spine board during patient transport only) must be maintained until spinal injury has been ruled out (Figure 3)
- vertebral injuries may be present without spinal cord injury; normal neurologic exam does not exclude spinal injury
- cord may be injured despite normal C-spine x-ray (SCIWORA = spinal cord injury without radiologic abnormality)
- injuries can include: complete/incomplete transection, cord edema, spinal shock

History
- mechanism of injury, previous deficits, SAMPLE
- neck pain, paralysis/weakness, paresthesia

Physical Exam
- ABCs
- abdominal: ecchymosis, tenderness
- neurological: complete exam, including mental status
- spine: maintain neutral position, palpate C-spine; log roll, then palpate T-spine and L-spine, assess rectal tone
  - when palpating, assess for tenderness, muscle spasm, bony deformities, step-off, and spinous process malalignment
- extremities: check capillary refill, suspect thoracolumbar injury with calcaneal fractures

Investigations
- bloodwork: CBC, electrolytes, Cr, glucose, coagulation profile, cross and type, toxicology screen
- imaging
  - full C-spine x-ray series for trauma (AP, lateral, odontoid)
- thoracolumbar x-rays
  - AP and lateral views
  - indications
    - patients with C-spine injury
    - unconscious patients (with appropriate mechanism of injury)
For Alert (GCS Score = 15) and Stable Trauma Patients where C-Spine Injury is a Concern

1. Any high-risk factor that mandates radiography?
   - Age ≥ 65 yr
   - Dangerous mechanism*
   - Paresthesia in extremities

2. Any one low-risk factor that allows safe assessment of ROM?
   - Simple rear-end MVC†
   - Sitting position in ED
   - Ambulatory at any time
   - Delayed onset of neck pain§
   - Absence of midline C-spine tenderness

3. Able to actively rotate neck? >45º left and right

   - Yes
   - No radiography

   - No
   - Radiography

   - Unable

Suspected C-Spine Injury
** based on mechanism of injury (e.g. MVC, fall, sports)

History: midline neck pain, numbness or paresthesia, presence of distracting pain, head injury, intoxication, loss of consciousness or past history of spinal mobility disorder

Physical exam: posterior neck spasm, tenderness or crepitus, any neurologic deficit or autonomic dysfunction, altered mental state

Management of Cord Injury
- immobilize
- evaluate ABCs
- treat neurogenic shock (maintain sBP >100 mmHg)
- insert NG and Foley catheter
- high dose steroids: methylprednisolone 30 mg/kg bolus, then 5.4 mg/kg/h drip, start within 6-8 h of injury (controversial and recently has less support)
- complete imaging of spine and consult spine service if available
- continually reassess high cord injuries as edema can travel up cord
- if cervical cord lesion, watch for respiratory insufficiency
  - low cervical transection (C5-T1) produces abdominal breathing (phrenic innervation of diaphragm still intact)
  - high cervical cord injury (above C4) may require intubation and ventilation
- treatment: warm blanket, Trendelenburg position (occasionally), volume infusion, consider vasopressors

Approach to C-Spine X-Rays
- 3-view C-spine series is the screening modality of choice
  1. lateral C1-T1 ± swimmer’s view
  - lateral view is best, identifies 90-95% of injuries
  2. odontoid view (open mouth or oblique submental view)
  - examine the dens for fractures
  - if unable to rule out fracture, repeat view or consider CT or plain film tomography
  - examine lateral aspects of C1 and spacing relative to C2
  3. AP view
  - alignment of spinous processes in the midline
  - spacing of spinous processes should be equal
  - check vertebral bodies and facet dislocations

Flexible, submental, anteroposterior (AP) views of the cervical spine are the preferred imaging method for the evaluation of suspected cervical spine injuries.

Prevertebral soft tissue swelling is only 49% sensitive for injury
Table 6. Interpretation of Lateral View: The ABCS

A Adequacy and Alignment
- Must see C1 to C7-T1 junction; if not, downward traction of shoulders, swimmer’s view, bilateral supine obliques, or CT scan needed
- Lines of contour in children <8 yr of age, can see physiologic subluxation of C2 on C3, and C3 on C4, but the spino-laminal line is maintained
- Fanning of spinous processes suggests posterior ligamentous disruption
- Widening of facet joints
- Check atlanto-occipital joint
- Line extending inferiorly from clivus should transect odontoid
- Atlanto-axial articulation, widening of predental space (normal: <3 mm in adults, <5 mm in children) indicates injury of C1 or C2

B Bones
- Height, width, and shape of each vertebral body
- Pedicles, facets, and laminae should appear as one – doubling suggests rotation

C Cartilage
- Intervertebral disc spaces – wedging anteriorly or posteriorly suggests vertebral compression

S Soft Tissues
- Widening of retropharyngeal (normal: <7 mm at C1-4, may be wide in children <2 yr on expiration) or retrotracheal spaces (normal: <22 mm at C6-T1, <14 mm in children <5 yr)

Sequelea of C-Spine Fractures
- see Neurosurgery, NS33
  - acute phase of SCI
    - spinal shock: absence of all voluntary and reflex activity below level of injury
      - decreased reflexes, no sensation, flaccid paralysis below level of injury, lasting days to months
    - neurogenic shock: loss of vasomotor tone, SNS tone
      - watch for: hypotension (lacking SNS), bradycardia (unopposed PNS), poikilothermia (lacking SNS so no shunting of blood from extremities to core)
      - occurs within 30 min of SCI at level T6 or above, lasting up to 6 wk
      - provide airway support, fluids, atropine (for bradycardia), vasopressors for BP support
  - chronic phase of SCI
    - autonomic dysreflexia: in patients with an SCI at level T6 or above
      - signs and symptoms: pounding headache, nasal congestion, feeling of apprehension or anxiety, visual changes, dangerously increased sBP and dBP
      - common triggers
        - GU causes: bladder distention, urinary tract infection, and kidney stones
        - GI causes: fecal impaction or bowel distension
      - treatment: monitoring and controlling BP, prior to addressing causative issue

Chest Trauma
- two types: those found and managed in 1º survey and those found and managed in 2º survey

Table 7. Life-Threatening Chest Injuries Found in 1º Survey

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway Obstruction</td>
<td>Anxiety, stridor, hoarseness, altered mental status, Apnea, cyanosis</td>
<td>Do not wait for ABG to intubate</td>
</tr>
<tr>
<td>Tension Pneumothorax</td>
<td>Respiratory distress, tachycardia, distended neck veins, cyanosis, asymmetry of chest wall motion, Tracheal deviation away from pneumothorax, Percussion hyperresonance, Unilateral absence of breath sounds</td>
<td>Non-radiographic diagnosis</td>
</tr>
</tbody>
</table>

Trauma to the chest accounts for 50% of trauma deaths
80% of all chest injuries can be managed non-surgically with simple measures such as intubation, chest tubes, and pain control
Table 7. Life-Threatening Chest Injuries Found in 1st Survey (continued)

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Open Pneumothorax</td>
<td>• Air entering chest from wound rather than trachea</td>
<td>• Gunshot or other wound (hole &gt;2/3 tracheal diameter) = exit wound</td>
</tr>
<tr>
<td>Massive Hemothorax</td>
<td>• &gt;1,500 cc blood loss in chest cavity</td>
<td>• Pain, flat neck veins, shock</td>
</tr>
<tr>
<td>Flail Chest</td>
<td>• Free-floating segment of chest wall due to &gt;2 rib fractures, each at 2 sites</td>
<td>• Paradoxical movement of flail segment</td>
</tr>
<tr>
<td>Cardiac Tamponade</td>
<td>• Clinical diagnosis</td>
<td>• Penetrating wound (usually)</td>
</tr>
<tr>
<td></td>
<td>• Pericardial fluid accumulation impairing ventricular function</td>
<td>• Pepper’s triad: hypotension, distended neck veins, muffled heart sounds</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Tachycardia, tachypnea</td>
</tr>
</tbody>
</table>

Table 8. Potentially Life-Threatening Chest Injuries Found in 2nd Survey

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Contusion</td>
<td>• Blunt trauma to chest</td>
<td>• CXR: areas of opacification of lung within 6 h of trauma</td>
</tr>
<tr>
<td></td>
<td>• Interstitial edema impairs compliance and gas exchange</td>
<td></td>
</tr>
<tr>
<td>Ruptured Diaphragm</td>
<td>• Blunt trauma to chest or abdomen (e.g. high lap belt in MVC)</td>
<td>• CXR: abnormality of diaphragm/lower lung fields/NG tube placement</td>
</tr>
<tr>
<td>Esophageal Injury</td>
<td>• Usually penetrating trauma (pain out of proportion to degree of injury)</td>
<td>• CXR: mediastinal air (not always)</td>
</tr>
<tr>
<td>Aortic Tear</td>
<td>• 90% tear at subclavian (near ligamentum arteriosum), most die at scene</td>
<td>• CXR, CT scan, transesophageal echo, aortography (gold standard)</td>
</tr>
<tr>
<td></td>
<td>• Salvageable if diagnosis made rapidly</td>
<td>• See sidebar for CXR features</td>
</tr>
<tr>
<td>Blunt Myocardial Injury (rare)</td>
<td>• Blunt trauma to chest (usually in setting of multi-system trauma and therefore difficult to diagnose)</td>
<td>• ECG: dysrhythmias, ST changes</td>
</tr>
<tr>
<td></td>
<td>• Physical exam: overlying injury, e.g. fractures, chest wall contusion</td>
<td>• Patients with a normal ECG and normal hemodynamics never get dysrhythmias</td>
</tr>
</tbody>
</table>

Other Potentially Life-Threatening Injuries Related to the Chest

Penetrating Neck Trauma
- includes all penetrating trauma to the three zones of the neck
- management: injuries deep to platysma require further evaluation by angiography, contrast CT, or surgery
- do not explore penetrating neck wounds except in the OR
Airway Injuries
• always maintain a high index of suspicion
• larynx
  ▪ history: strangulation, direct blow, blunt trauma, any penetrating injury involving platysma
  ▪ triad: hoarseness, subcutaneous emphysema, palpable fracture
  ▪ other symptoms: hemoptysis, dyspnea, dysphonia
  ▪ investigations: CXR, CT scan, arteriography (if penetrating)
• management
  ▪ airway: manage early because of edema
  ▪ C-spine may also be injured, consider mechanism of injury
  ▪ surgical: tracheotomy vs. repair

trachea/bronchus
• frequently missed
• history: deceleration, penetration, increased intra-thoracic pressure, complaints of dyspnea, hemoptysis
• examination: subcutaneous air, Hamman’s sign (crunching sound synchronous with heart beat)
• CXR: mediastinal air, persistent pneumothorax or persistent air leak after chest tube inserted for pneumothorax
• management: surgical repair if >1/3 circumference

Abdominal Trauma
• two mechanisms
  ▪ blunt: usually causes solid organ injury (spleen = most common, liver = 2nd)
  ▪ penetrating: usually causes hollow organ injury or liver injury (most common)

BLUNT TRAUMA
• results in two types of hemorrhage: intra-abdominal and retroperitoneal
• adopt high clinical suspicion of bleeding in multi-system trauma

History
• mechanism of injury, SAMPLE history

Physical Exam
• often unreliable in multi-system trauma, wide spectrum of presentations
  ▪ slow blood loss not immediately apparent
  ▪ tachycardia, tachypnea, oliguria, febrile, hypotension
  ▪ other injuries may mask symptoms
  ▪ serial examinations are required
• abdomen
  ▪ inspect: contusions, abrasions, seat-belt sign, distention
  ▪ auscultate: bruits, bowel sounds
  ▪ palpate: tenderness, rebound tenderness, rigidity, guarding
  ▪ DRE: rectal tone, blood, bone fragments, prostate location
  ▪ placement of NG, Foley catheter should be considered part of the abdominal exam
• other systems to assess: cardiovascular, respiratory (possibility of diaphragm rupture), genitourinary, pelvis, back/neurological

Investigations
• labs: CBC, electrolytes, coagulation, cross and type, glucose, Cr, CK, lipase, amylase, liver enzymes, ABG, blood EtOH, β-hCG, U/A, toxicology screen

Table 9. Imaging in Abdominal Trauma
<table>
<thead>
<tr>
<th>Imaging</th>
<th>Strengths</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td>Chest (looking for free air under diaphragm, diaphragmatic hernia, air-fluid levels), pelvis, cervical, thoracic, lumbar spines</td>
<td>Soft tissue not well visualized</td>
</tr>
<tr>
<td>CT Scan</td>
<td>Most specific test</td>
<td>Radiation exposure 20x more than x-ray Cannot use if hemodynamic instability</td>
</tr>
<tr>
<td>Diagnostic Peritoneal Lavage (rarely used)</td>
<td>Most sensitive test Tests for intra-peritoneal bleed</td>
<td>Cannot test for retroperitoneal bleed or diaphragmatic rupture Cannot distinguish lethal from trivial bleed Results can take up to 1 h</td>
</tr>
<tr>
<td>Ultrasound: FAST</td>
<td>Identifies presence/absence of free fluid in peritoneal cavity RAPID exam: less than 5 min Can also examine pericardium and pleural cavities</td>
<td>NOT used to identify specific organ injuries If patient has ascites, FAST will be falsely positive</td>
</tr>
</tbody>
</table>

Criteria for Positive Lavage
• >10 cc gross blood
• Bile, bacteria, foreign material
• RBC count >100,000 x 10^6/L
• WBC >500 x 10^6/L
• Amylase >175 IU
imaging must be done if
- equivocal abdominal examination, altered sensorium, or distracting injuries (e.g. head trauma, spinal cord injury resulting in abdominal anesthesia)
- unexplained shock/hypotension
- multiple trauma patients who must undergo general anesthesia for orthopedic, neurosurgical, or other injuries
- fractures of lower ribs, pelvis, spine
- positive FAST

**Management**
- general: ABCs, fluid resuscitation, and stabilization
- surgical: watchful waiting vs. laparotomy
- solid organ injuries: decision based on hemodynamic stability, not the specific injuries
- hemodynamically unstable or persistently high transfusion requirements: laparotomy
- hollow organ injuries: laparotomy
- even if low suspicion of injury: admit and observe for 24 h

**Penetrating Trauma**
- high risk of gastrointestinal perforation and sepsis
- history: size of blade, calibre/distance from gun, route of entry
- local wound exploration under direct vision may determine lack of peritoneal penetration (not reliable in inexperienced hands) with the following exceptions:
  - thoracoabdominal region (may cause pneumothorax)
- back or flanks (muscles too thick)

**Etiology**
- blunt trauma: often associated with pelvic fractures
  - upper tract
    - renal
    - contusions (minor injury – parenchymal ecchymoses with intact renal capsule)
    - parenchymal tears/laceration: non-communicating (hematoma) vs. communicating (urine extravasation, hematuria)
  - ureter: rare, at uretero-pelvic junction
- lower tract
  - bladder
  - extraperitoneal rupture of bladder from pelvic fracture fragments
  - intraperitoneal rupture of bladder from trauma and full bladder
  - urethra
  - posterior urethral injuries: MVCs, falls, pelvic fractures
  - anterior urethral injuries: blunt trauma to perineum, straddle injuries/direct strikes
- external genitalia
- penetrating trauma
  - damage to: kidney, bladder, ureter (rare), external genitalia
- acceleration/deceleration injury
  - renal pedicle injury: high mortality rate (laceration and thrombosis of renal artery, renal vein, and their branches)
- iatrogenic
  - ureter and urethra (from instrumentation)

**History**
- mechanism of injury
- hematuria (microscopic or gross), blood on underwear
- dysuria, urinary retention
- history of hypotension

**Physical Exam**
- abdominal pain, flank pain, CVA tenderness, upper quadrant mass, perineal lacerations
- DRE: sphincter tone, position of prostate, presence of blood
- scrotum: ecchymoses, lacerations, testicular disruption, hematomas
- bimanual exam, speculum exam
extraperitoneal bladder rupture: pelvic instability, suprapubic tenderness from mass of urine or extravasated blood
intraperitoneal bladder rupture: acute abdomen
urethral injury: perineal ecchymosis, scrotal hematoma, blood at penile meatus, high riding prostate, pelvic fractures

**Investigations**
- urethra: retrograde urethrography
- bladder: U/A, CT scan, urethrogram ± retrograde cystoscopy ± cystogram (distended bladder + post-void)
- ureter: retrograde ureterogram
- renal: CT scan (best, if hemodynamically stable), intravenous pyelogram

**Management**
- urology consult
- renal
  - minor injuries: conservative management
    - bedrest, hydration, analgesia, antibiotics
  - major injuries: admit
    - conservative management with frequent reassessments, serial U/A ± re-imaging
    - surgical repair (exploration, nephrectomy): hemodynamically unstable or continuing to bleed >48 h, major urine extravasation, renal pedicle injury, all penetrating wounds and major lacerations, infections, renal artery thrombosis
- ureter
  - ureterouretostomy
- bladder
  - extraperitoneal
    - minor rupture: Foley drainage x 10-14 d
    - major rupture: surgical repair
  - intraperitoneal
    - drain abdomen and surgical repair
- urethra
  - anterior: conservative, if cannot void → Foley or suprapubic cystostomy and antibiotics
  - posterior: suprapubic cystostomy (avoid catheterization) ± surgical repair

**Orthopedic Injuries**
- Orthopedics (Shoulder OR11, Knee OR32, Wrist OR20, Ankle OR38)

**Goals of ED Treatment**
- diagnose potentially life/limb threatening injuries
- reduce and immobilize fractures (cast/splint) as appropriate
- provide adequate pain relief
- arrange proper follow-up if necessary

**History**
- use SAMPLE
- mechanism of injury may be very important

**Physical Exam**
- look (inspection): “SEADS” Swelling, Erythema, Atrophy, Deformity, Skin changes (e.g. bruises)
- feel (palpation): all joints/bones for local tenderness, swelling, warmth, crepitus, joint effusions, subtle deformity
- move: joints affected plus those above and below injury – active ROM preferred to passive
  - neurovascular status: distal to injury (before and after reduction)

**LIFE- AND LIMB-THREATENING INJURIES**

<table>
<thead>
<tr>
<th>Life-Threatening Injuries (usually blood loss)</th>
<th>Limb-Threatening Injuries (usually interruption of blood supply)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major pelvic fractures</td>
<td>Fracture/dislocation of ankle (talar AVN)</td>
</tr>
<tr>
<td>Traumatic amputations</td>
<td>Crush injuries</td>
</tr>
<tr>
<td>Massive long bone injuries (beware of fat emboli)</td>
<td>Compartment syndrome</td>
</tr>
<tr>
<td>Vascular injury proximal to knee/elbow</td>
<td>Open fractures</td>
</tr>
<tr>
<td></td>
<td>Dislocations of knee/hip</td>
</tr>
<tr>
<td></td>
<td>Fractures above knee/elbow</td>
</tr>
</tbody>
</table>
Open Fractures
- communication between fracture site and external surface of skin – increased risk of osteomyelitis
- remove gross debris, irrigate, cover with sterile dressing – formal irrigation and debridement often done in the OR
- control bleeding with pressure (no clamping)
- splint
- antibiotics (1st generation cephalosporin and aminoglycoside) and tetanus prophylaxis
- must secure definitive surgical care within 6-8 h

Vascular Injuries
- realign limb/apply longitudinal traction and reassess pulses (e.g. Doppler probe)
- surgical consult
- direct pressure if external bleeding

Compartment Syndrome
- increased interstitial pressure in an anatomical “compartment” (forearm, calf) with little room for expansion, resulting in decreased perfusion and potential muscle/nerve necrosis
- clinical diagnosis: maintain a high index of suspicion
  - pain out of proportion to the injury
  - pain worse with passive stretch
  - look for “the 6 Ps”
- requires prompt decompression: remove constrictive casts, dressings; fasciotomy may be needed emergently

UPPER EXTREMITY INJURIES
- anterior shoulder dislocation
  - axillary nerve (lateral aspect of shoulder) and musculocutaneous nerve (extensor aspect of forearm) at risk
  - seen on lateral view: humeral head anterior to glenoid
    - reduce (traction, scapular manipulation), immobilize in internal rotation, repeat x-ray, out-patient follow-up with orthopedics
    - with forceful injury, look for fracture
  - Colles’ fracture
    - distal radius fracture with dorsal displacement from “Fall on Outstretched Hand” (FOOSH)
    - AP film: shortening, radial deviation, radial displacement
    - lateral film: dorsal displacement, volar angulation
    - reduce, immobilize with splint, out-patient follow-up with orthopedics or immediate orthopedic referral if complicated fracture
    - if involvement of articular surface, emergent orthopedic referral
  - scaphoid fracture
    - tenderness in anatomical snuff box, pain on scaphoid tubercle, pain on axial loading of thumb
    - negative x-ray: thumb spica splint, repeat x-ray in 1 wk ± CT scan/bone scan
    - positive x-ray: thumb spica splint x 6-8 wk, repeat x-ray in 2 wk
    - risk of AVN of scaphoid if not immobilized
    - outpatient orthopedics follow-up

LOWER EXTREMITY INJURIES
- ankle and foot fractures
  - see Ottawa Ankle and Foot Rules
- knee injuries
  - see Ottawa Knee Rules
  - avulsion of the base of 5th metatarsal
    - occurs with inversion injury
    - supportive tensor or below knee walking cast for 3 wk
- calcaneal fracture
  - associated with fall from height
  - associated injuries may involve ankles, knees, hips, pelvis, lumbar spine

Figure 9. Ottawa knee rules

A knee x-ray examination is required only for acute injury patients with one or more of:
- Age 55 yr or older
- Tenderness at head of fibula
- Isolated tenderness of patella
- Inability to flex to 90º
- Inability to bear weight both immediately and in the ED (four steps)

Adapted from: Stiell IG, et al. JAMA 1997;278:2075-2079
Wound Management

Goals of ED Treatment
- identify injuries and stop any active bleeding – direct pressure
- manage pain
- wound examination and exploration (history and physical)
- cleansing ± antibiotic and tetanus prophylaxis
- closure and dressing

Tetanus Prophylaxis
- both tetanus toxoid (Td) and immunoglobulin (TIG) are safe in pregnancy

<table>
<thead>
<tr>
<th>Immunization History</th>
<th>Non-Tetanus Prone Wounds</th>
<th>Tetanus Prone Wounds¹</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Td²</td>
<td>TIG³</td>
</tr>
<tr>
<td>Uncertain or &lt;3 doses</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3 or more, none for &gt;10 yr</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3 or more, 5 to 10 yr ago</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3 or more, &lt;4 yr ago</td>
<td>No</td>
<td>No</td>
</tr>
</tbody>
</table>

¹ wounds >6 h old, >1 cm deep, puncture wounds, avulsions, wounds resulting from missiles, crush wounds, burns, frostbite, wounds contaminated with dirt, feces, soil, or saliva
² 0.5 mL IM tetanus and diphtheria toxoids (Td), adsorbed
³ tetanus immune globulin (TIG), 250 units deep IM
Source: MMWR 2001;50;418-427; MMWR 1991;40:1-52

Bruises
- non-palpable = ecchymosis
- palpable collection (not swelling) = hematoma following blunt trauma
- assess for coagulopathy (e.g. liver disease), anticoagulant use

Abrasions
- partial to full thickness break in skin
- management
  - clean thoroughly with brush to prevent foreign body impregnation ± local anesthetic antiseptic ointment (Polysporin® or Vaseline®) for 7 d for facial and complex abrasions
  - tetanus prophylaxis

Lacerations
- see Plastic Surgery, PL8
- consider every structure deep to a laceration injured until proven otherwise
- in hand injury patients, include the following in history: handedness, occupation, mechanism of injury, previous history of injury

Accuracy of Ottawa Ankle Rules to Exclude Fractures of the Ankle and Mid-Foot: Systematic Review
BMJ 2003;326;417
This systematic review and meta-analysis of 27 studies including 15,581 patients evaluated the sensitivity and specificity of the Ottawa Ankle Rules for excluding fractures of the ankle and mid-foot.
Results: The pooled likelihood ratio of a negative result (obtaining a false negative) among those with a fracture was determined to be 0.08 for both the ankle and mid-foot.
Conclusions: The Ottawa Ankle Rules provide an accurate instrument for excluding fractures of the ankle and mid-foot with a sensitivity of almost 100% and a specificity of 26%. The use of this instrument can reduce the number of unnecessary radiographs.

Acute Treatment of Contusions
RICE
Rest
Ice
Compression
Elevation

High Risk Factors for Infection
Wound Factors
- Puncture wounds
- Crush injuries
- Wounds >12 h old
- Hand or foot wounds
- Immunocompromised
Patient Factors
- Age >50 yr
- Prosthetic joints or valves (risk of endocarditis)

Suture Use and Duration

<table>
<thead>
<tr>
<th>Suture Use and Duration</th>
<th>Close with Nylon or Other Nonabsorbable Suture</th>
<th>Approx. Duration (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Face</td>
<td>6-0</td>
<td>5</td>
</tr>
<tr>
<td>Not Joint</td>
<td>4-0</td>
<td>7</td>
</tr>
<tr>
<td>Joint</td>
<td>3-0</td>
<td>10</td>
</tr>
<tr>
<td>Scap</td>
<td>4-0</td>
<td>7</td>
</tr>
<tr>
<td>Mucous Membrane</td>
<td>absorbable (vicryl) N/A</td>
<td></td>
</tr>
</tbody>
</table>

N.B. Patients on steroid therapy may need sutures for longer periods of time
• physical exam
  • think about underlying anatomy
  • examine tendon function actively against resistance and neurovascular status distally
  • clean and explore under local anesthetic; look for partial tendon injuries
  • x-ray or U/S wounds if a foreign body is suspected (e.g. shattered glass) and not found when exploring wound (remember: not all foreign bodies are radioopaque), or if suspect intra-articular involvement

• management
  • disinfect skin/use sterile techniques
  • irrigate copiously with normal saline
  • analgesia ± anesthesia
  • maximum dose of lidocaine
    • 7 mg/kg with epinephrine
    • 5 mg/kg without epinephrine
  • in children, topical anesthetics such as LET (lidocaine, epinephrine and tetracaine), and in selected cases a short-acting benzodiazepine (midazolam or other agents) for sedation and amnesia are useful
  • secure hemostasis
  • evacuate hematomas, debride non-viable tissue, remove hair and foreign bodies
  • ± prophylactic antibiotics (consider for animal/human bites, intraoral lesion, or puncture wounds to the foot)
  • suture unless: delayed presentation (>6-8 h), puncture wound, mammalian bite, crush injury, or retained foreign body
  • take into account patient and wound factors when considering suturing
  • advise patient when to have sutures removed
  • cellulitis and necrotizing fasciitis (see Plastic Surgery, PL14)

Table 12. Selected Differential Diagnosis of Abdominal Pain

<table>
<thead>
<tr>
<th>Emergent</th>
<th>Usually Less Emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>Diverticulitis, gastroenteritis, GERD, esophagitis, gastritis, IBS</td>
</tr>
<tr>
<td>Hepatobiliary</td>
<td>Biliary, cholecystitis, hepatitis</td>
</tr>
<tr>
<td>Genital</td>
<td>Female: tubo-ovarian abscess, ovarian cyst, salpingitis, endometriosis, Male: epididymitis, prostatitis</td>
</tr>
<tr>
<td>Urinary</td>
<td>Pyelonephritis, Renal colic, cystitis</td>
</tr>
<tr>
<td>CVS</td>
<td>MI, aortic dissection, AAA, Pericarditis</td>
</tr>
<tr>
<td>Respiriology</td>
<td>PE, empyema, Pneumonia</td>
</tr>
<tr>
<td>Metabolic</td>
<td>DKA, sickle cell crisis, toxin, Addisonian crisis</td>
</tr>
<tr>
<td>Other</td>
<td>Significant trauma, acute angle closure glaucoma</td>
</tr>
<tr>
<td>Abdominal wall injury, herpes zoster, psychiatric, abscess, meningitis, adenitis</td>
<td></td>
</tr>
</tbody>
</table>

• differential can be focused anatomically by location of pain: RUQ, LUQ, RLQ, LLQ, epigastric, periumbilical, diffuse

History
• pain: OPQRST
• review symptoms from GU, gynecological, GI, respiratory, and CV systems
• abdominal trauma/surgeries most recent colonoscopy

Physical Exam
• vitals, abdominal (including DRE, CVA tenderness), pelvic/genital, respiratory, and cardiac exams as indicated by history

Investigations
• ABCs, do not delay management and consultation if patient unstable
• CBC, electrolytes, glucose, BUN/Cr, U/A ± liver enzymes, LFTs, lipase, β-hCG, ECG, troponins, ± VBG/lactate
• AXR: look for calcifications, free air, gas pattern, air fluid levels

Approach to Common ED Presentations

Abdominal Pain

Be vigilant: very young, elderly, alcoholics, immunosuppressed patients often present atypically

Old age, pregnancy (T3), and chronic corticosteroid use can blunt peritoneal findings, so have an increased level of suspicion for an intra-abdominal process in these individuals

Unstable patients should not be sent for imaging

If elevated AST and ALTT
Think hepatocellular injury
AST > ALT: alcohol-related
ALT > AST: viral, drug, toxin

If elevated ALP and GGT
Think biliary tree obstruction
• CXR upright: look for pneumoperitoneum (free air under diaphragm), lung disease
• U/S: biliary tract, ectopic pregnancy, AAA, free fluid
• CT: trauma, AAA, pancreatitis, nephro-/urothiasis, appendicitis, and diverticulitis

Management
• NPO, IV, NG tube, analgesics, consider antibiotics and anti-emetics
• growing evidence that small amounts of opioid analgesics improve diagnostic accuracy of physical exam of surgical abdomen
• consult as necessary: general surgery, vascular surgery, gynecology, etc.

Disposition
• admission: surgical abdomen, workup of significant abnormal findings, need for IV antibiotics or pain control
• discharge: patients with a negative lab and imaging workup who improve clinically during their stay; instruct the patient to return if severe pain, fever, or persistent vomiting develops

Acute Pelvic Pain

Etiology
• gynecological
  ▪ second most common gynecological complaint (after vaginal bleeding)
  ▪ ovaries: ruptured ovarian cyst (most common cause of pelvic pain), ovarian abscess, ovarian torsion (rare, 50% will have ovarian mass)
  ▪ fallopian tubes: salpingitis, tubal abscess, hydrosalpinx
  ▪ uterus: leiomyomas (uterine fibroids) – especially with torsion of a pedunculated fibroid or in a pregnant patient (degeneration), PID, endometriosis
  ▪ other: ectopic pregnancy (ruptured/expanding/leaking), spontaneous abortion (threatened or incomplete), endometriosis and dysmenorrhea, sexual or physical abuse
• non-gynecological (see causes of lower abdominal pain above)

History and Physical Exam
• pain: OPQRST
• associated symptoms: vaginal bleeding, discharge, dyspareunia, bowel or bladder symptoms
• pregnancy and sexual history
• vitals
• gynecological exam: assess for cervical motion tenderness/”chandelier sign” (suggests PID)
• abdominal exam

Investigations
• β-hCG for all women of childbearing age
• CBC and differential, electrolytes, glucose, Cr, BUN, G&S, PTT/INR
• vaginal and cervical swabs for C&S during physical exam
• pelvic and abdominal U/S: evaluate adnexa, thickness of endometrium, pregnancy, free fluid or masses in the pelvis
• Doppler flow studies for ovarian torsion

Management
• general: analgesia, determine if admission and consults are needed
• specific
  ▪ ovarian cysts
    ▪ unruptured or ruptured and hemodynamically stable: analgesia and follow-up
    ▪ ruptured with significant hemoperitoneum: may require surgery
  ▪ ovarian torsion: surgical detorsion or removal of ovary
  ▪ uncomplicated leiomyomas, endometriosis, and secondary dysmenorrhea can usually be treated on an outpatient basis, discharge with gynecology follow-up
  ▪ PID: requires broad spectrum antibiotics

Disposition
• referral: gynecological or obstetrical causes requiring surgical intervention, requiring admission, or oncological in nature
• admission: patients requiring surgery, IV antibiotics/pain management
• discharge: negative workup and resolving symptoms; give clear instructions for appropriate follow-up

Analgesia in Patients with Acute Abdominal Pain
Cochrane database of systemic reviews 2011, issue 1. Art. No.:CD005660
Study: systematic review of all RCTs of adult patients with acute abdominal pain (AAP) comparing use of opioid analgesia during initial evaluation with placebo. Included in the review:8 RCTs.
Population: patients age >14 with non traumatic AAP <1 week duration.
Intervention: six trials used morphine, one trial used Tramadol, one study Papaveretum as analgesia.
Main outcome measure: diagnostic accuracy.
Results: there were no significant differences in the physical examination among the groups or when comparing by drug. There were no significant differences in rate of ‘incorrect diagnosis’ among the groups.
Conclusion: the use of analgesia for acute abdominal pain does not increase risk of diagnostic error and does not mask clinical findings.

Gynecological Causes of Pelvic Pain
• Ovarian cyst
• Dysmenorrhea
• Mittelschmerz
• Endometriosis
• Ovarian torsion
• Uterine Fibroids/neoplasm
• Adnexal neoplasm
• PID + cervicitis

U/S is the preferred imaging modality in the assessment of acute pelvic pain
Altered Level of Consciousness

Definitions
- altered mental status: collective, non-specific term referring to change in cognitive function, behaviour, or attentiveness, including:
  - delirium (see Psychiatry, PS20)
  - dementia (see Psychiatry, PS21)
  - lethargy: state of decreased awareness and alertness (patient may appear wakeful)
  - stupor: unresponsiveness but rousable
  - coma: a sleep-like state, not rousable to consciousness

Figure 11. Etiology of coma

MANAGEMENT OF ALTERED LOC

History
- obtain collateral from family, friends, police, paramedics, old chart, MedicAlert® bracelet, etc.
- onset and progression
  - antecedent trauma, seizure activity, fever
  - abrupt onset suggests CNS hemorrhage/ischemia or cardiac cause
  - progression over hours to days suggests progressive CNS lesion or toxic/metabolic cause
- determine patient's baseline LOC
- past medical history (e.g. similar episode, depression, overdose)

Physical Exam
- ABCs, vitals including temperature; cardiac, respiratory, abdominal exams
- complete neurological exam; in particular, examination of the eyes (pupil size and reactivity)
  - use the GCS to evaluate LOC (see Initial Patient Assessment/Management, ER2)

Investigations
- blood work
  - rapid blood sugar, CBC, electrolytes, Cr, BUN, LFTs, glucose, serum osmolality, VBG, PT/PTT/INR, troponins
  - serum EtOH, acetaminophen, and salicylate levels
- imaging
  - CXR, CT head
- other tests
  - ECG, U/A, UTox

Diagnosis
- administer appropriate universal antidotes
  - thiamine 100 mg IV if history of EtOH or patient looks malnourished
  - one ampule D50W IV if low blood sugar on finger-prick
  - naloxone 0.4-2 mg IV or IM if opiate overdose suspected
- distinguish between structural and toxic-metabolic coma
  - structural coma
    - pupils, extraocular movements, and motor findings, if present, are usually asymmetric
    - look for focal or lateralizing abnormalities
  - Toxic/Metabolic
    - Major organ failure
    - Electrolyte/Endocrine
    - Toxins/Temperature
    - Acid disorders
    - Base disorders
    - decreased Oxygen level
    - Lactate
    - Insulin/Infection (sepsis)
    - Cardiac/hyperCalcemia
  - Primary CNS disease/trauma
    - Bilateral cerebral hemispheres (affecting cognition)
    - Brainstem (affecting reticular activating system)
    - Compression
      - Supra/infratentorial tumour
      - Sub/epidural hematoma
  - Direct
    - Brainstem infarct or hemorrhage

In general, intubate if GCS <8; but ability to protect airway is primary consideration
• toxic-metabolic coma
  • dysfunction at lower levels of the brainstem (e.g. caloric unresponsiveness)
  • respiratory depression in association with an intact upper brainstem (e.g. equal and reactive pupils; see exceptions in Table 13)
  • extraocular movements and motor findings are symmetric or absent
• essential to re-examine frequently because status can change rapidly
• diagnosis may become apparent only with the passage of time
  • delayed deficit after head trauma suggestive of epidural hematoma (characteristic “lucid interval”)

Table 13. Toxic-Metabolic Causes of Fixed Pupils

<table>
<thead>
<tr>
<th>Dilated</th>
<th>Dilated to Normal</th>
<th>Constricted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anoxia</td>
<td>Hypothermia</td>
<td>Cholinergic agents (e.g. organophosphates)</td>
</tr>
<tr>
<td>Anticholinergic agents (e.g. atropine, TCAs)</td>
<td>Barbiturates</td>
<td>Opiates (e.g. heroin), except meperidine</td>
</tr>
<tr>
<td>Methanol (rare)</td>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Cocaine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid withdrawal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amphetamines</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinogens</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Disposition
• admission: if ongoing decreased LOC, admit to service based on tentative diagnosis, or transfer patient if appropriate level of care not available
• discharge: readily reversible alteration of LOC; ensure adequate follow-up care available

Chest Pain

Table 14. Differential Diagnosis for Chest Pain

<table>
<thead>
<tr>
<th>Emergent</th>
<th>Usually Less Emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>MI, unstable angina, aortic dissection, cardiac tamponade, arrhythmia</td>
</tr>
<tr>
<td>Respirology</td>
<td>PE, pneumothorax</td>
</tr>
<tr>
<td>GI</td>
<td>Pneumonia, pleural effusion, malignancy</td>
</tr>
<tr>
<td>Esophageal rupture, pneumomediastinum</td>
<td>Peptic ulcer disease, esophagitis, GERD, esophageal spasm, pancreatitis, cholecystitis</td>
</tr>
<tr>
<td>MSK</td>
<td>Rib fracture, costochondritis</td>
</tr>
<tr>
<td>Other</td>
<td>Herpes zoster, psychiatric/panic attack</td>
</tr>
</tbody>
</table>

History and Physical Exam
• OPQRST, previous episodes and change in pattern
• cardiac risk factors (HTN, DM, dyslipidemia, smoking, FHx)
• vitals, cardiac, respiratory, peripheral vascular, abdominal exams

Investigations
• CBC, electrolytes, Cr, BUN, glucose, PTT/INR
• ECG: always compare with previous; may be normal in up to 50% of PE and acute MI
• CXR: compare with previous

Management and Disposition
• ABCs, O₂, cardiac monitors, IV access
• treat underlying cause and involve consultants as necessary
• consider further observation/monitoring if unclear diagnosis or risk of dysrhythmia
• discharge: patients with a low probability of life-threatening illness due to resolving symptoms and negative workup; arrange follow-up and instruct to return if SOB or increased chest pain develops

Life-Threatening Causes of Chest Pain
PET MAP
P E Sophageal rupture
T amponade
M I/angina
Aortic dissection
Pneumothorax

Angina Characteristics
1. Retrosternal location
2. Provoked by exertion
3. Relieved by rest or nitroglycerin

Risk for CAD
3/3 = “typical angina” - high risk
2/3 = intermediate risk for women >50 yr, all men
1/3 = Intermediate risk in men >40 yr, women >60 yr

Imaging is necessary for all suspected aortic dissections, regardless of BP
Table 15. Comparison of Chest Pain Diagnoses

<table>
<thead>
<tr>
<th>Classic History</th>
<th>Classic Findings</th>
<th>Diagnostic Investigations</th>
<th>Management and Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Coronary Syndrome</strong></td>
<td>New or worsening pattern of retrosternal squeezing/pain, radiation to arm/neck, dyspnea, worsened by exercise, relieved by rest N/V; syncope</td>
<td>ECG: ischemia (15 lead if no wave; AV node involvement or inferior MI), serial troponin I (sensitive 6-8h after onset), CK-MB, CXR</td>
<td>ABCs, aspirin, anticoagulation and emergent cardiology consult to consider percutaneous intervention or thrombolytic</td>
</tr>
<tr>
<td><strong>Pulmonary Embolism</strong></td>
<td>Pleuritic chest pain (75%), dyspnea; risk factors for venous thromboembolism</td>
<td>Tachycardia, hypoxemia; evidence of DVT</td>
<td>Wells’s criteria: D-dimer, CT pulmonary angiogram*, V/Q scan; leg dopplers, CXR</td>
</tr>
<tr>
<td><strong>Acute Pericarditis</strong></td>
<td>Viral prodrome, anterior precordial pain, pleuritic, relieved by sitting up and leaning forward</td>
<td>Triphasic friction rub</td>
<td>ECG: sinus tachycardia, diffuse ST elevation, PR depression in II, III, avF and V4-6; reciprocal PR elevation and ST depression in AVR ± V1; echocardiography</td>
</tr>
<tr>
<td><strong>Pneumothorax</strong></td>
<td>Trauma or spontaneous pleuritic chest pain often in tall, thin, young male athlete</td>
<td>Hemithorax with decreased/absent breath sounds, hyper-resonance; deviated trachea and hemodynamic compromise</td>
<td>Clinical diagnosis CXR: PA, lateral, expiratory views – lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view</td>
</tr>
<tr>
<td><strong>Aortic Dissection</strong></td>
<td>Sudden severe tearing retrosternal or midscapular pain ± focal pain/neuropathic loss in extremities in context of HTN</td>
<td>HTN; systolic BP difference &gt;20 mmHg or pulse deficit between arms; aortic regurgitant murmur</td>
<td>CT angiography CXR: PA, lateral, expiratory views – lung edge, loss of lung markings, tracheal shift; deep sulcus sign on supine view</td>
</tr>
<tr>
<td><strong>Cardiac tamponade</strong></td>
<td>Dyspnea, cold extremities, ± chest pain; often a recent cardiac intervention or symptoms of malignancy, connective tissue disease</td>
<td>Beck’s triad - hypotension, elevated JVP, muffled heart sounds; tachycardia, pulsus paradoxus &gt;10 mmHg</td>
<td>Clinical diagnosis CXR: may show cardiomegaly, evidence of trauma</td>
</tr>
<tr>
<td><strong>Esophageal Rupture</strong></td>
<td>Sudden onset severe pain after endoscopy, forceful vomiting, labour, or convulsion, or in context of corrosive injury or cancer</td>
<td>Subcutaneous emphysema, findings consistent with sepsis</td>
<td>CT: pleural effusion (75%), pneumomediastinum; CT or water soluble contrast esophagogram</td>
</tr>
<tr>
<td><strong>Esophagitis or GERD</strong></td>
<td>Frequent heartburn, acid reflux, dysphagia, relief with antacids</td>
<td>Oral thrush or ulcers (rare)</td>
<td>None acutely</td>
</tr>
<tr>
<td><strong>Herpes Zoster</strong></td>
<td>Abnormal skin sensation – itching/tinging/pain – preceding rash by 1-5d</td>
<td>None if early; maculopapular rash developing into vesicles and pustules that crust</td>
<td>Clinical diagnosis; direct immunofluorescence assay</td>
</tr>
<tr>
<td><strong>MSK</strong></td>
<td>History of injury</td>
<td>Reproduction of symptoms with movement or palpation (not specific – present in 25% of MI)</td>
<td>MSK injury or fracture on X-rays</td>
</tr>
<tr>
<td><strong>Anxiety</strong></td>
<td>Symptoms of anxiety, depression, history of psychiatric disorder; may coexist with physical disease</td>
<td>Tachycardia, diaphoresis, tremor</td>
<td>Diagnosis of exclusion</td>
</tr>
</tbody>
</table>
### Table 16. Common Life-Threatening ECG Changes

<table>
<thead>
<tr>
<th>Pathology</th>
<th>ECG Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dysrhythmia</strong></td>
<td></td>
</tr>
<tr>
<td>a) Torsades de pointes</td>
<td>Ventricular complexes in upward-pointing and downward-pointing continuum (250-350 bpm)</td>
</tr>
<tr>
<td>b) Ventricular tachycardia</td>
<td>6 or more consecutive premature ventricular beats (150-250 bpm)</td>
</tr>
<tr>
<td>c) Ventricular flutter</td>
<td>Smooth sine wave pattern of similar amplitude (250-350 bpm)</td>
</tr>
<tr>
<td>d) Ventricular fibrillation</td>
<td>Erratic ECG tracing, no identifiable waves</td>
</tr>
<tr>
<td><strong>Conduction</strong></td>
<td></td>
</tr>
<tr>
<td>a) 2nd degree heart block (Mobitz Type II)</td>
<td>PR interval stable, some QRSs dropped</td>
</tr>
<tr>
<td></td>
<td>Total AV dissociation, but stable P-P and R-R intervals</td>
</tr>
<tr>
<td>b) 3rd degree heart block</td>
<td>Prolonged QRS complex (&gt;0.12 s)</td>
</tr>
<tr>
<td>c) Left bundle branch block</td>
<td>May see ST elevation</td>
</tr>
<tr>
<td></td>
<td>Difficult to interpret, new LBBB is considered STEMI equivalent</td>
</tr>
<tr>
<td><strong>Ischemia</strong></td>
<td></td>
</tr>
<tr>
<td>a) STEMI</td>
<td>ST elevation in leads associated with injured area of heart and reciprocal lead changes (depression)</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>a) Hyperkalemia</td>
<td>Tall T waves</td>
</tr>
<tr>
<td>b) Hypokalemia</td>
<td>P wave flattening</td>
</tr>
<tr>
<td></td>
<td>QRS complex widening and flattening</td>
</tr>
<tr>
<td></td>
<td>U waves appear</td>
</tr>
<tr>
<td></td>
<td>Flattened T waves</td>
</tr>
<tr>
<td><strong>Digitalis Toxicity</strong></td>
<td>Gradual downward curve of ST</td>
</tr>
<tr>
<td><strong>Syndromes</strong></td>
<td>At risk for AV blocks and ventricular irritability</td>
</tr>
<tr>
<td>a) Brugada</td>
<td>RBBB with ST elevation in V1, V2, and V3</td>
</tr>
<tr>
<td>b) Wellens</td>
<td>Susceptible to deadly dysrhythmias, including VFib</td>
</tr>
<tr>
<td>c) Long QT syndrome</td>
<td>QT interval longer than ½ of cardiac cycle</td>
</tr>
<tr>
<td></td>
<td>Predisposed to ventricular dysrhythmias</td>
</tr>
</tbody>
</table>

### Headache

- see Neurology, N45

#### Etiology

**the common**
- common migraine (without aura)/classic migraine (with aura)
  - common: unilateral, throbbing, aggravated by activity, moderate/severe, N/V, photo-/phonophobia
  - classic: varied aura symptoms, e.g. lights in vision, pins and needles, loss of vision, dysarthria
  - abortive treatment: fluids, NSAIDs, antiemetics, antiepileptic drugs, vasoactive medications
  - family doctor to consider prophylactic treatment
- tension/muscular headache
  - mild-moderate headache with gradual onset lasting minutes to days
  - bilateral-frontal or nuchal-occipital
  - increased with stress, sleep deprivation
  - treatment: modify stressor(s), local measures, NSAIDs, tricyclic antidepressants

**the deadly**
- subarachnoid hemorrhage (SAH) (see Neurosurgery, NS18)
  - sudden onset, “worst headache of life” maximum intensity within minutes
  - increased pain with exertion, N/V, meningeval signs
  - diagnosis
    - new generation CT 100% sensitive if read by neuroradiologist within 6h of onset
    - LP if suspected SAH and normal CT after 6h
  - management: urgent neurosurgery consult
  - increased ICP
    - worse in morning, when supine or bending down, with cough or Valsalva
    - physical exam: neurological deficits, cranial nerve palsies, papilledema
• diagnosis: CT head  
• meningitis (see Infectious Diseases, ID18)  
• flu-like symptoms (fever, N/V, malaise), meningeal signs, petechial rash  
• altered LOC and confusion  
• rule out increased ICP; if CT head or normal mental status, no neurological signs and no papilledema, then do LP for diagnosis  
• treatment: early empiric antibiotics ± acyclovir, steroid therapy  
• temporal arteritis (causes significant morbidity, blindness) (see Ophthalmology, OP38)  
• unilateral scalp tenderness, jaw claudication, visual disturbances  
• temporal artery biopsy is gold standard for diagnosis  
• associated with polymyalgia rheumatica  
• treatment: high-dose steroids immediately if suspected

Disposition  
• admission: if underlying diagnosis is critical or emergent, if there are abnormal neurological findings, if patient is elderly or immunocompromised (atypical presentation), or if pain is refractory to oral medications  
• discharge: assess for risk of narcotic misuse; most patients can be discharged with appropriate analgesia and follow-up with their family physician; instruct patients to return for fever, vomiting, neurologic changes, or increasing pain

Joint and Back Pain

JOINT PAIN (see Rheumatology, RH3)  
• rule out life threatening causes: septic joint (see Orthopedics, OR10)

History and Physical Exam  
• associated symptoms: fever, constitutional symptoms, skin lesions, conjunctivitis, urethritis  
• patterns of joint involvement: polyarticular vs. monoarticular, symmetric vs. asymmetric  
• inflammatory symptoms: prolonged morning stiffness; stiffness and pain ease through the day, midday fatigue, soft tissue swelling  
• non-inflammatory symptoms: stiffness short lived after inactivity, short duration stiffness in the morning, pain increases with activity  
• assess ROM, presence of joint effusion, warmth  
• assess for localized joint pain, erythema, warmth, swelling with pain on active ROM, inability to bear weight, fever; may indicate presence of septic joint

Investigations  
• blood work: CBC, ESR, CRP, WBC, INR/PTT, blood cultures, urate  
• joint x-ray ± contralateral joint for comparison  
• bedside U/S to identify effusion  
• joint aspirate send for: WBC, protein, glucose, Gram stain, crystals

Management  
• septic joint: IV antibiotics ± joint decompression and drainage  
• antibiotics can be started empirically if septic arthritis cannot be ruled out  
• crystalline synovitis: NSAIDs at high dose, colchicine within first 24 h, corticosteroids  
• do not use allopurinol, as it may worsen acute attack  
• acute polyarthritis: NSAIDs, analgesics (acetylsalicylic ± opioids), local or systemic corticosteroids  
• osteoarthritis: NSAIDs, acetylsalicylic  
• soft tissue pain: allow healing with enforced rest ± immobilization  
• non-pharmacologic treatment: local heat or cold, electrical stimulation, massage  
• pharmacologic: oral analgesics, NSAIDs, muscle relaxants, corticosteroid injections, topical agents

BACK PAIN (see Family Medicine, FM40)  
• rule out vascular emergencies: aortic dissection, AAA, PE, MI, retroperitoneal bleed  
• rule out spinal emergencies using red flags (see sidebar): osteomyelitis, cauda equina, epidual abscess or hematoma  
• evaluate risk for fracture (osteoporosis, age), infection (IV drug user, recent spinal intervention, immunosuppression), cancer, vascular causes (cardiac risk factors)  
• typical benign back pain is moderate, dull, aching, worse with movement or cough  
• palpate spine for bony tenderness; precordial, respiratory, abdominal and neurological exams guided by history  
• reserve imaging for suspicion of emergencies, metastases, and patients at high risk of fracture, infection, cancer, or vascular causes

CT Head within 6 h is 100% Sensitive for Diagnosis of Subarachnoid Hemorrhage (SAH)  
BMJ 2008;336(7657):1359 A meta-analysis of 7 RCTs examined the effectiveness of parenteral corticosteroids use after administration of standard abortive therapy. The primary outcome was recurrence of migraine within 72 hours of treatment. All trials compared single-dose parenteral dexamethasone with placebo. Results showed dexamethasone and placebo provided similar acute pain reduction (weighted mean difference 0.37, 95% CI 0.2-0.5, I²=0). Dexamethasone was, however, more effective than placebo in reducing recurrence rates (RR 0.34, 95% CI 0.2-0.5). Conclusions: when added to standard abortive therapy for migraine headaches, single dose of parenteral dexamethasone is associated with 26% RR in recurrent headaches (NNT=9).

Which Patients can Safely Undergo Lumbar Puncture Without Screening CT?  
Arch Intern Med 1999;159(22):2681-2685  
Study: a prospective study to identify patients who can safely undergo LP without CT.  
Population: 113 patients, age > 18 yd, needing urgent LP as determined by ED physicians.  
Intervention: all patients were examined before CT by staff physicians. Physician examiners involved in the study then recorded the presence or absence of 10 clinical findings and answered 8 questions regarding the patient’s past medical history and recorded their perceived likelihood that LP would be contraindicated.  
Main outcome measure: results of non-contrast CTs interpreted by staff radiologist.  
Results: 2.7% of patients had lesions on CT that contraindicated LP. Overall, clinical impression had the highest predictive value in identifying patients with contraindications to LP (1+16.8). When used in aggregate—altering mental status, focal neurological examination and papilledema were three statistically significant identified predictors of new intracranial lesion-related LP (1). When used alone these predictors were inadequate.  
Conclusion: given the low prevalence of lesions that contraindicate LP, screening CT solely to establish the safety of LP provides minimal extra information. Physicians can rely on their clinical judgement and the three predictors.

Meningitis  
• Do not delay IV antibiotics for LP  
• Deliver first dose of dexamethasone with or before first dose of antibiotic therapy

Parenteral Dexamethasone for Preventing Recurrence of Acute Severe Migraine Headache  
BMC 2003;316(9757):1359  
A meta-analysis of 1 RCTs examined the effectiveness of parenteral corticosteroids use after administration of standard abortive therapy. The primary outcome was recurrence of migraine within 72 hours of treatment. All trials compared single-dose parenteral dexamethasone with placebo. Results showed dexamethasone and placebo provided similar acute pain reduction (weighted mean difference 0.37, 95% CI 0.2-0.5, I²=0). Dexamethasone was, however, more effective than placebo in reducing recurrence rates (RR 0.34, 95% CI 0.2-0.5). Conclusions: when added to standard abortive therapy for migraine headaches, single dose of parenteral dexamethasone is associated with 26% RR in recurrent headaches (NNT=9).

CT Head within 6 h is 100% Sensitive for Diagnosis of Subarachnoid Hemorrhage (SAH)  
BMJ 2012;346:e140717  
Study: a prospective multicentre cohort study was conducted in 11 tertiary care emergency departments across Canada to measure the sensitivity of CT head in the evaluation of ED patients for SAH.  
Population: neurologically intact adults who presented with new onset non-traumatic headache reaching maximum intensity in less than one hour while head CT as part of their diagnostic workup to rule out SAH.  
Design: patients were deemed positive for SAH if they had subarachnoid blood on CT or xanthochromia in the CSF or red blood cells in the final tube of CSF collected. Some patients with normal results on CT received LP at the discretion of the treating physician. Unless patients had a negative result on LP or a definitive cause for the headache identified through neuroimaging patients were followed for six months to ascertain their outcome.  
Main Outcome Measures: Results of CT interpreted by staff radiologist.  
Results: Overall sensitivity of CT for detecting subarachnoid hemorrhage was 92.9%, specificity 100%. Subgroup analysis revealed 100% sensitivity for patients scanned within 6 h of headache onset.  
Conclusion: CT is extremely sensitive in identifying subarachnoid hemorrhage when it is carried out within 6 h of headache onset.

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**Seizures**

- see Neurology: N18

**Definition**
- paroxysmal alteration of behaviour and/or EEG changes resulting from abnormal, excessive activity of neurons
- status epilepticus: continuous or intermittent seizure activity for greater than 5 min without regaining consciousness

**Categories**
- generalized seizure (consciousness always lost): tonic/clonic, absence, myoclonic, atonic
- partial seizure (focal): simple partial, complex partial
- causes: primary seizure disorder, structural (trauma, intracranial hemorrhage, infection, increased ICP), metabolic disturbance (hippo-/hyperglycemia, hippo-/hypernatremia, hypocalcemia, hypomagnesemia, toxins/drugs)
- differential diagnosis: syncope, pseudoseizures, migraines, movement disorders, narcolepsy/cataplexy, myoclonus

**History**
- from patient and bystander: flaccid and unconscious, often with deep rapid breathing
- preceding aura, rapid onset, loss of bladder/bowel control, tongue-biting (sides of the tongue)
- length of seizure and post-ictal symptoms

**Physical Exam**
- injuries to head and spine and bony prominences (e.g. elbows), tongue laceration, aspiration, urinary incontinence

**Table 17. Concurrent Investigation and Management of Status Epileptics**

<table>
<thead>
<tr>
<th>Timing</th>
<th>Steps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate</td>
<td>Protect airway with positioning; intubate if airway compromised or elevated ICP&lt;br&gt;Monitor: vital signs, ECG, oximetry; bedside blood glucose&lt;br&gt;Establish IV access&lt;br&gt;Benzodiazepine - IV lorazepam 0.1 mg/kg up to 4 mg/dose at 2 mg/min preferred over IV diazepam 0.15 mg/kg up to 10 mg/dose at 5 mg/min; repeat at 5 min if ineffective&lt;br&gt;Fluid resuscitation: Give 50 mL 50% glucose (preceded by thiamine 100 mg IM in adults)&lt;br&gt;Obtain blood samples for glucose, CBC, electrolytes, Ca⁺², Mg⁺², toxins, and antiepileptic drug levels; consider prolactin, β-hCG&lt;br&gt;Vasopressor support if sBP &lt; 90 or MAP &lt; 70 mmHg</td>
</tr>
<tr>
<td>Urgent</td>
<td>Establish second IV line, urinary catheter&lt;br&gt; If status persists, phenytoin 20 mg/kg IV at 25-50 mg/min in adults; may give additional 10 mg/kg IV 10 minutes after loading infusion&lt;br&gt; If seizure resolves, antiepileptic drug still required to prevent recurrence&lt;br&gt; EEG monitoring to evaluate for non-convulsive status epilepticus</td>
</tr>
<tr>
<td>Refractory</td>
<td>If status persists after maximum doses above, consult ICU and start one or more of: Phenytoin 20 mg/kg IV at 50 mg/min&lt;br&gt; Midazolam 0.2 mg/kg IV loading dose and 0.05-0.5 mg/kg/h&lt;br&gt; Propofol 2-5 mg/kg IV loading dose then 2-10 mg/kg/h</td>
</tr>
<tr>
<td>Post-Seizure</td>
<td>Investigate underlying cause: consider CT, LP, MRI, intracranial pressure monitoring</td>
</tr>
</tbody>
</table>

Note: All interventions should be done as soon as possible
Adapted from Brophy et al. Guidelines for the Evaluation and Management of Status Epilepticus. Neurocrit Care 2012;17:3-23

**Disposition**
- decision to admit or discharge should be based on the underlying disease process identified
  - if a patient has returned to baseline function and is neurologically intact, then consider discharge with outpatient follow-up
  - first-time seizure patients being discharged should be referred to a neurologist for follow-up
  - admitted patients should generally have a neurology consult
  - patient should not drive until medically cleared (local regulations vary)
  - complete notification form to appropriate authority regarding ability to drive
  - warn regarding other safety concerns (e.g. no swimming, bathing children alone, etc.)
Shortness of Breath

- see Respirology, R3 and Cardiology and Cardiac Surgery, C5

### Table 18. Differential Diagnosis for Dyspnea

<table>
<thead>
<tr>
<th>High Mortality/Morbidity</th>
<th>Usually Less Emergent</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
</tr>
<tr>
<td>Airway obstruction (Foreign body, epiglottitis, abscess, anaphylaxis)</td>
<td>Chronic obstructive, interstitial or restrictive lung disease</td>
</tr>
<tr>
<td>Pneumo/hemothorax</td>
<td>Plural effusion</td>
</tr>
<tr>
<td>Gas exchange –Pulmonary edema, PE, pneumonia, AECOPD</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiac</strong></td>
<td></td>
</tr>
<tr>
<td>CHF, MI, valvular disease, tamponade, arrhythmia</td>
<td>Chronic CHF, Angina</td>
</tr>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
</tr>
<tr>
<td>Metabolic acidosis NYD, carbon monoxide inhalation</td>
<td>Anemia, Hemoglobinopathy</td>
</tr>
<tr>
<td><strong>Neuromuscular</strong></td>
<td></td>
</tr>
<tr>
<td>Myasthenia gravis, diaphragmatic paralysis</td>
<td>CNS lesion, primary muscle weakness</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Anxiety, deconditioning</td>
</tr>
</tbody>
</table>

**History and Physical Exam**

- acute SOB is often due to a relatively limited number of conditions; associated symptoms and signs are key to the appropriate diagnosis
  - substernal chest pain with cardiac ischemia
  - fever, cough, and sputum with respiratory infections
  - urticaria with anaphylaxis
  - wheezing with acute bronchospasm
  - environmental or occupational exposures
- dyspnea may be the sole complaint and the physical exam may reveal few abnormalities (e.g. PE, pneumothorax)
- vitals including pulse oximetry
  - wheeze (airway) vs. crackles (parenchymal), JVP, and murmurs

**Investigations**

- blood work
  - CBC and differential (hematocrit to exclude anemia), electrolytes, consider VBG
  - serial cardiac enzymes and ECG if considering cardiac source
  - Wells scores to consider appropriateness of d-dimer
- imaging
  - CXR (hyperinflation and bullous disease suggestive of obstructive lung disease, or changes in interstitial markings consistent with inflammation, infection, or interstitial fluid)
  - CT chest usually is not indicated in the initial evaluation of patients with dyspnea, but can be valuable in patients with interstitial lung disease, occult emphysema, or chronic thromboembolic disease (i.e. PE)

**Management of Life-Threatening Dyspnea NYD**

- see Primary and Secondary Surveys, ER2, ER5
- treat underlying cause

**Disposition**

- the history and physical exam lead to accurate diagnoses in patients with dyspnea in approximately two-thirds of cases; the decision to admit or discharge should be based on the underlying disease process identified
  - consider intubation in CO₂ retainers (e.g. COPD)
- if discharging, organize follow-up and educate regarding signs to return to hospital

---

**Syncope**

**Definition**

- sudden, transient loss of consciousness and postural tone with spontaneous recovery
- usually caused by generalized cerebral or reticular activating system hypoperfusion

**Etiology**

- cardiogenic: dysrhythmia, outflow obstruction (e.g. PE, pulmonary HTN), MI, valvular disease
- non-cardiogenic: peripheral vascular (hypovolemia), vasovagal, cerebrovascular disorders, CNS, metabolic disturbances (e.g. EtOH intoxication)
History
- gather details from witnesses, and clarify patient's experience (e.g. dizziness, ataxia, or true syncope)
  - two key historical features: prodrome and situation
- distinguish between syncope and seizure (see Neurology, N19)
  - some patients may have myoclonic jerks with syncope – NOT a seizure
  - signs and symptoms during presyncope, syncope, and postsyncope
  - past medical history, drugs
  - think anatomically in differential; pump (heart), blood, vessels, brain
- syncope is cardiogenic until proven otherwise if
  - there is sudden loss of consciousness with no warning or prodrome
  - syncope is accompanied by chest pain

Physical Exam
- postural BP and HR
- cardiovascular, respiratory, and neurological exam
- examine for signs of trauma caused by syncopal episode

Investigations
- ECG (tachycardia, bradycardia, blocks, Wolff-Parkinson White, long QT interval), bedside glucose
- blood work: CBC, electrolytes, BUN/Cr, ABGs, troponin, Ca²⁺, Mg²⁺, β-hCG
- consider toxicology screen

Management
- ABCs, IV, O₂, monitor
- cardiogenic syncope: admit to medicine/cardiology
- low risk syncope: discharge with follow-up as indicated by cause (non-cardiogenic syncope may still be admitted)

Disposition
- decision to admit is based on etiology
- most patients will be discharged
- on discharge, instruct patient to follow up with family physician
  - educate about avoiding orthostatic or situational syncope
  - evaluate the patient for fitness to drive or work
- patients with recurrent syncope should avoid high-risk activities (e.g. driving)

Sexual Assault

Epidemiology
- 1 in 4 women and 1 in 10 men will be sexually assaulted in their lifetime; only 7% are reported

General Approach
- ABCs, treat acute, serious injuries; physician priority is to treat medical issues and provide clearance
- ensure patient is not left alone and provide ongoing emotional support
- obtain consent for medical exam and treatment, collection of evidence, disclosure to police (notify police as soon as consent obtained)
- Sexual Assault Kit (document injuries, collect evidence) if <72 h since assault
- label samples immediately and pass directly to police
- offer community crisis resources (e.g. shelter, hotline)
- do not report unless victim requests or if <16 yr old (legally required)

History
- ensure privacy for the patient – others should be asked to leave
- questions to ask: who, when, where did penetration occur, what happened, any weapons, or physical assault?
- post-assault activities (urination, defecation, change of clothes, shower, douche, etc.)
- gynecologic history
  - gravidity, parity, last menstrual period
  - contraception use
- last voluntary intercourse (sperm motile 6-12 h in vagina, 5 d in cervix)
- medical history: acute injury/illness, chronic diseases, psychiatric history, medications, allergies, etc.
Physical Exam
- never re-traumatize a patient with the examination
- general examination
  - mental status
  - sexual maturity
  - patient should remove clothes and place in paper bag
  - document abrasions, bruises, lacerations, torn frenulum/broken teeth (indicates oral penetration)
- pelvic exam and specimen collection
  - ideally before urination or defecation
  - examine for seminal stains, hymen, signs of trauma
  - collect moistened swabs of dried seminal stains
  - pubic hair combings and cuttings
  - speculum exam
    - lubricate with water only
    - vaginal lacerations, foreign bodies
    - Pap smear, oral/cervical/rectal culture for gonorrhea and chlamydia
    - posterior fornix secretions if present or aspiration of saline irrigation
    - immediate wet smear for motile sperm
    - air-dried slides for immotile sperm, acid phosphatase, ABO group
  - fingernail scrapings and saliva sample from victim

Investigations
- VDRL: repeat in 3 mo if negative
- serum β-hCG
- blood for ABO group, Rh type, baseline serology (e.g. hepatitis, HIV)

Management
- involve local/regional sexual assault team
- medical
  - suture lacerations, tetanus prophylaxis
  - gynecology consult for foreign body, complex lacerations
  - assumed positive for gonorrhea and chlamydia
    - management: azithromycin 1 g PO x 1 dose (alt: doxycycline 100 mg PO bid x 7 d) and cefixime 800 mg PO x 1 dose (alt: ceftriaxone 1 g IM x 1 dose)
  - may start prophylaxis for hepatitis B and HIV
  - pre and post counselling for HIV testing
  - pregnancy prophylaxis offered
    - levonorgestrel 0.75 mg PO STAT, repeat within 12 h (Plan B+)
  - psychological
    - high incidence of psychological sequelae
    - have victim change and shower after exam completed

Disposition
- discharge if injuries/social situation permit
- follow-up with physician in rape crisis centre within 24 h
- best if patient does not leave ED alone

DOMESTIC VIOLENCE
- women are usually the victims, but male victimization also occurs
- identify the problem (need high index of suspicion)
  - suggestive injuries (bruises, sprains, abrasions, occasionally fractures, burns, or other injuries; often inconsistent with history provided)
  - somatic symptoms (chronic and vague complaints)
  - psychosocial symptoms
  - clinician impression (your ‘gut feeling’, e.g. overbearing partner that won’t leave patient’s side)
- if disclosed, be supportive and assess danger
  - patient must consent to follow-up investigation/reporting (unless for children)

Management
- treat injuries and document findings
- ask about sexual assault and children at home (encourage notification of police)
- safety plan with good follow-up with family doctor/social worker

Risk of Sexually Transmitted Disease after Sexual Assault
- Gonorrhea: 6-18%
- Chlamydia: 4-17%
- Syphilis: 0.5-3%
- HIV: <1%
Medical Emergencies

Anaphylaxis and Allergic Reactions

Etiology
- Anaphylaxis is an exaggerated immune-mediated hypersensitivity reaction that leads to systemic histamine release, increased vascular permeability, and vasodilation; regardless of the etiology, the presentation and management of anaphylactic reactions are the same
  - Allergic (re-exposure to allergen)
  - Non-allergic (e.g. exercise-induced)

Diagnostic Criteria
- Anaphylaxis is highly likely with any of
  1. Acute onset of an illness (min to hrs) with involvement of the skin, mucosal tissue and at least one of
     - Respiratory compromise (e.g. dyspnea, wheeze, stridor, hypoxemia)
     - Hypotension/end-organ dysfunction (e.g. hypotonia, collapse, syncope, incontinence)
  2. Two or more of the following after exposure to a LIKELY allergen for that patient (min to hrs)
     - Involvement of the skin-mucosal tissue
     - Respiratory compromise
     - Hypotension or associated symptoms
     - Persistent gastrointestinal symptoms (e.g. crampy abdominal pain, vomiting)
  3. Hypotension after exposure to a KNOWN allergen for that patient (min to hrs)
     - Management is also appropriate in cases which do not fulfill criteria, but who have had previous episodes of anaphylaxis
     - Life-threatening differentials for anaphylaxis include asthma and septic shock
     - Angioedema may mimic anaphylaxis but tends not to improve with standard anaphylaxis treatment

Management
1. Immediate initial management (call for help and perform concurrently)
   - Give 0.3-0.5 mL of 1:1,000 epinephrine IM to lateral thigh, may repeat q5-15min
   - If ABCs compromised or LOC, manage and consult ICU immediately
   - O2
   - Give bolus 1 L crystalloid IV (IO if necessary); Trendelenberg position
   - Have continuous pulse oximetry and telemetry; frequent BP monitoring
   - Remove causative agent if possible
2. Secondary treatment
   - Diphenhydramine (Benadryl®) 50 mg IM or IV q4-6h
   - Ranitidine 50 mg IV
   - Methylprednisolone 125 mg IV (dose depending on severity)
   - Salbutamol (Ventolin®) via nebulizer if bronchospasm

Disposition
- Monitor for 4-6 h in ED (minimum) and arrange follow-up with family physician in 24-48 h
- Can have second phase (biphasic) reaction up to 48 h later, patient may need to be supervised
- Educate patient on avoidance of allergens
- Medications
  - H1 antagonist (cetirizine 10 mg PO OD or Benadryl® 50 mg PO q4-6h x3d)
  - H2 antagonist (ranitidine 150 mg PO OD x3d)
  - Corticosteroid (prednisone 50 mg PO OD) x5d to prevent secondary reaction

Asthma
- See Respiriology, R7
- Chronic inflammatory airway disease with episodes of bronchospasm and inflammation resulting in reversible airflow obstruction

History and Physical
- Find cause of asthma exacerbation (viral, environmental, etc.)
- History of asthma control; severity of exacerbations (ICU, intubation history)
- Signs of respiratory distress
- Vitals, specifically O2

Investigations
- Peak flow meter
- ± ABG if in severe respiratory distress
- CXR if diagnosis in doubt to rule out pneumonia, pneumothorax, etc.
Table 19. Asthma Assessment and Management

<table>
<thead>
<tr>
<th>Classifications</th>
<th>History and Physical Exam</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Arrest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Imminent</strong></td>
<td>• Exhausted, confused, diaphoretic, cyanotic</td>
<td>• 100% O2, cardiac monitor, IV access</td>
</tr>
<tr>
<td></td>
<td>• Silent chest, ineffective respiratory effort</td>
<td>• Intubate (consider induction with ketamine)</td>
</tr>
<tr>
<td></td>
<td>• Decreased HR, RR&gt;30, pCO₂&gt;45 mmHg</td>
<td>• β-agonist: nebulizer 5 mg continually</td>
</tr>
<tr>
<td></td>
<td>• O₂ sat &lt;90% despite supplemental O₂</td>
<td>• Anticholinergics: nebulizer 0.5 mg x 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• IV steroids: methylprednisolone 125 mg</td>
</tr>
<tr>
<td><strong>Severe Asthma</strong></td>
<td>• Agitated, diaphoretic, laboured respirations</td>
<td>• Anticipate need for intubation</td>
</tr>
<tr>
<td></td>
<td>• Speaking in words</td>
<td>• Similar to above management</td>
</tr>
<tr>
<td></td>
<td>• No relief from β-agonist</td>
<td>• Magnesium sulphate 2 g IV</td>
</tr>
<tr>
<td></td>
<td>• O₂ sat &lt;90%, FEV₁ &lt;50%</td>
<td>• O₂ to achieve O₂ sat &gt;92%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• β-agonist: MDI or nebulizer q5min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Steroids: prednisone 40-60 mg PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Anticholinergics (Atrovent®) MDI or nebs x3</td>
</tr>
<tr>
<td><strong>Moderate Asthma</strong></td>
<td>• SOB at rest, cough, congestion, chest tightness</td>
<td>• O₂ to achieve O₂ sat &gt;92%</td>
</tr>
<tr>
<td></td>
<td>• Speaking in phrases</td>
<td>• β-agonist</td>
</tr>
<tr>
<td></td>
<td>• Inadequate relief from β-agonist</td>
<td>• Monitor FEV₁</td>
</tr>
<tr>
<td></td>
<td>• FEV₁ 50-80%</td>
<td>• Consider steroids (MDI or PO)</td>
</tr>
<tr>
<td><strong>Mild Asthma</strong></td>
<td>• Exertional SOB/cough with some nocturnal symptoms</td>
<td>• β-agonist</td>
</tr>
<tr>
<td></td>
<td>• Difficulty finishing sentences</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• FEV₁ &gt;80%</td>
<td></td>
</tr>
</tbody>
</table>

Disposition
- β-agonist MDI with aerochamber 2-4 puffs q2-4h until symptoms controlled, then prn
- inhaled corticosteroids with aerochamber if not already prescribed
- prednisone 30-60 mg/d for 7 d with no taper
- counsel on medication adherence and educate on use of aerochamber
- follow-up with primary care physician

Cardiac Dysrhythmias

- see Cardiology and Cardiac Surgery, C17

Bradydysrhythmias and AV Conduction Blocks
- AV conduction blocks
  - 1st degree: prolonged PR interval (>200 msec), no treatment required
  - 2nd degree
    - Mobitz I: gradual prolongation of PR interval then dropped QRS complex, usually benign
    - Mobitz II: PR interval constant with dropped QRS complex, can progress to 3rd degree AV block
  - 3rd degree: P wave unrelated to QRS complex, PP and RR intervals constant
    - atropine and transcutaneous pacemaker (atropine with caution)
    - if transcutaneous pacemaker fails consider dopamine, epinephrine IV
  - long-term treatment for Mobitz II and 3rd degree block – internal pacemaker
- sinus bradycardia (rate <60 bpm)
  - can be normal (especially in athletes)
  - causes: vagal stimulation, vomiting, myocardial infarction/ischemia, increased ICP, sick sinus node, hypothyroidism, drugs (e.g. β-blockers, CCBs)
  - treat if symptomatic (hypotension, chest pain)
    - acute: atropine ± transcutaneous pacing
    - sick sinus: transcutaneous pacing
    - drug induced: discontinue/reduce offending drug, consider antidotes

Supraventricular Tachydysrhythmias (narrow QRS)
- sinus tachycardia (rate >100 bpm)
  - causes: increased sympathetic tone, drugs, fever, hypotension, anemia, thyrotoxicosis, MI, PE, emotional, pain, etc.
  - search for and treat underlying cause, consider β-blocker if symptomatic
- regular rhythm (i.e. not sinus tachycardia)
  - vagal maneuvers (carotid massage, Valsalva), adenosine 6 mg IV push, if no conversion give 12 mg, can repeat 12 mg dose once
  - rhythm converts: probable re-entry tachycardia (AVNRT more common than AVRT)
    - monitor for recurrence
    - treat recurrence with adenosine or longer acting medications
  - rhythm does not convert: atrial flutter, ectopic atrial tachycardia, junctional tachycardia
    - rate control (diltiazem, β-blockers) and consult cardiology
- irregular rhythm
  - probable AFib, atrial flutter, or multifocal atrial tachycardia
  - rate control (diltiazem, β-blockers)
Atrial Fibrillation
• most common sustained dysrhythmia; no organized P waves (atrial rate >300/min), irregularly irregular heart rate, narrow QRS (typically)
• etiology: HTN, CAD, thyrotoxicosis, EtOH (holiday heart), valvular disease, pericarditis, cardiomyopathy, sick sinus syndrome
• treatment principles: stroke prevention, treat symptoms, identify/treat underlying cause
• decreases cardiac output by 20-30% (due to loss of organized atrial contractions)
• acute management
  • if unstable: immediate synchronized cardioversion
  • if onset of AFib is >48 h: rate control, anticoagulate 3 wk prior to and 4 wk after cardioversion, or do transesophageal echocardiogram to rule out clot
  • if onset <48 h or already anticoagulated: may cardiovert
• electrical cardioversion: synchronized direct current (DC) cardioversion
• chemical cardioversion: procainamide, flecainide, propafenone
• long-term management: rate or rhythm control, consider anticoagulation (CHADS2 score, see Cardiology and Cardiac Surgery, C20)

Ventricular Tachydysrhythmias (wide QRS)
• VTach (rate usually 140-200 bpm)
  • definition: 3 or more consecutive ventricular beats at >100 bpm
  • etiology: CAD with MI is most common cause
  • treatment: sustained VTach (>30 s) is an emergency
    • hemodynamic compromise: synchronized DC cardioversion
    • no hemodynamic compromise: synchronized DC cardioversion, amiodarone, procainamide
  • VFib: call a code blue, follow ACLS for pulseless arrest
  • Torsades de pointes
    • looks like VTach but QRS ‘rotates around baseline’ with changing axis and amplitude (twisted ribbon)
    • etiology: prolonged QT due to drugs (e.g. quinidine, TCAs, erythromycin, quinolones), electrolyte imbalance (hypokalemia, hypomagnesemia), congenital
    • treatment
      • IV Mg2+, temporary overdrive pacing, isoproterenol
      • correct cause of prolonged QT

Chronic Obstructive Pulmonary Disease
• see Respirology, R9
• progressive development of irreversible airway obstruction, typically caused by smoking

History and Physical Exam
• acute exacerbation: episode of increased dyspnea, coughing, increase in sputum volume or purulence
• triggers: virus, pneumonia, urinary tract infection, PE, CHF, MI, drugs
• characterize previous episodes and hospitalizations, smoking history
• vital signs, level of consciousness, signs of respiratory distress, respiratory exam

Investigations
• CBC, electrolytes, ABG, CXR, ECG, PFTs

Management
• keep O2 sat 88-92% (be aware when giving O2 to chronic hypercapnic/CO2 retainers but do not withhold O2, if hypoxic)
• apply BiPAP if severe distress, arterial pH <7.35, or hypercapnic
• ipratropium is anticholinergic agent of choice, add salbutamol
• steroids: prednisolone 40 mg PO for 7-10 d
• antibiotics: TMP-SMX, cephalosporins, respiratory quinolones (if acute change in frequency, quantity, and colour of sputum production)
• if life-threatening, ICU admission for ventilation (chance of ventilation dependency)
• lower threshold to admit if comorbid illness

Disposition
• no guidelines for admission - based on clinical judgement and comorbidities
• if discharging, use antibiotics, tapering steroids, up to 4-6 puffs qid of ipratropium and salbutamol and organize follow-up
### Congestive Heart Failure

- see Cardiology and Cardiac Surgery, C36

#### Etiology
- decreased myocardial contractility: ischemia, infarction, cardiomyopathy, myocarditis
- pressure overload states: HTN, valve abnormalities, congenital heart disease
- restricted cardiac output: myocardial infiltrative disease, cardiac tamponade
- volume overload

#### Presentation
- left-sided heart failure
- dyspnea, decreased exercise tolerance, paroxysmal nocturnal dyspnea, orthopnea, nocturia, fatigue, possibly altered mental status, syncope, angina, systemic hypotension
- hypoxia, decreased air entry to lungs, rales, S3 or S4, pulmonary edema (on CXR), pleural effusion (usually right-sided)
- right-sided heart failure
- dependent bilateral pitting edema, JVP elevation, hepatic enlargement, ascites
- patients often present with a combination of right-sided and left-sided symptoms

#### Investigations
- blood work: CBC, electrolytes, AST, ALT, bilirubin, Cr, BUN, cardiac enzymes, brain natriuretic peptide
- CXR (see sidebar)
- ECG: look for MI, ischemia (ST elevation/depression, T-wave inversion)
- in CHF: LVH, atrial enlargement, conduction abnormalities
- ABG: if severe or refractory to treatment
- hypoxemia, hypercapnia and acidosis are signs of severe CHF
- echocardiogram: not usually used in emergency evaluation, previous results may aid in diagnosis
- may be precipitated by dysrhythmia (e.g. sudden onset AFib) – correct if new
- rule out serious differentials such as PE, pneumothorax, pneumonia/empyema, COPD exacerbation

#### Management (Acute)
- ABC, may require intubation if severe hypoxia
- sit upright, cardiac monitoring, and continuous pulse oximetry
- saline lock IV, Foley catheter (to follow effectiveness of diuresis)
- 100% O2 by mask
  - if poor response, may require BiPAP or intubation
- drugs
  - nitroglycerin 0.3 mg SL q5min prn ± topical nitroglycerine patch (0.2-0.8 mg/h)
  - if not responding or ischemia: 10-200 µg/min IV, titrate
  - diuretic if volume overloaded (e.g. furosemide 40-80 mg IV), use caution if cause is valvulopathy
  - morphine 1-2 mg IV prn
  - if hypotensive: dobutamine (2.5 µg/kg/min IV) or dopamine (5-10 µg/kg/min IV), titrate up to sBP 90-100 mmHg
  - ASA 160 mg chew and swallow
- treat precipitating factor
- cardiology or medicine consult

### Deep Vein Thrombosis and Pulmonary Embolism

- see Respiratory, R18

#### Risk Factors
- Virchow’s triad: alterations in blood flow (venous stasis), injury to endothelium, hypercoagulable state (including pregnancy, use of OCP, malignancy)
- clinical risk factors (see sidebar)

#### Presentation
- DVT: calf pain, leg swelling/erythema/edema, palpable cord on exam; can be asymptomatic
- PE: dyspnea, pleuritic chest pain, hemoptyis, tachypnea, cyanosis, hypoxia, fever
- clinical signs/symptoms are unreliable for diagnosis and exclusion of DVT/PE; investigation often needed
- calculate the PERC (PE rule out criteria) score to assess the need for PE workup before assessing the likelihood of a PE (Wells’ Criteria)
Investigations
• PERC score alone can rule out PE unless patient is pregnant
• Use Wells’ criteria for DVT and PE to guide investigations (Figures 12-14)
• ECG and CXR are useful to look for other causes (e.g. ACS, pneumonia)
• D-dimer is only useful if it is negative in low risk patients (highly sensitive)
• U/S has high sensitivity and specificity for proximal clot but only 73% sensitivity for DVT below the knee (may need to repeat in 1 wk)
• CT angiography has high sensitivity and specificity for PE, may also suggest other etiology
• V/Q scan useful in pregnancy, when CT angiography not available, or IV contrast contraindicated

Management of DVT/PE
• LMWH unless patient also has renal failure
  ▪ dalteparin 200 IU/kg SC q24h or enoxaparin 1.5 mg/kg SC q24h
  ▪ warfarin started at same time as LMWH (5 mg PO OD initially)
  ▪ LMWH discontinued when INR has been therapeutic (2-3) for 2 consecutive days
  ▪ early ambulation with analgesia is safe if appropriately anticoagulated
  ▪ rivaroxaban can be used in both acute management of symptomatic DVT or PE and extended treatment
  ▪ 15 mg PO bid for first 21 d; 20 mg PO daily for remaining treatment (taken with food at approximately the same time each day)
  ▪ IVC filter or surgical thrombectomy considered if anticoagulation is contraindicated
  ▪ often can be treated as outpatient, may require analgesia for chest pain (narcotic or NSAID)
  ▪ admit if hemodynamically unstable, require supplemental O2, major comorbidities, lack of sufficient social supports, unable to ambulate, need invasive therapy
  ▪ referral to medicine for coagulopathy and malignancy workup
  ▪ long-term anticoagulation
    ▪ if reversible risk factor: 3-6 mo of warfarin
    ▪ idiopathic VTE: may need longer term warfarin (5 yr or more)

Figure 12. Approach to suspected DVT

Figure 13. Approach to suspected PE
Diabetic Emergencies

- see Endocrinology, E11

**Diabetic Ketoacidosis**
- severe insulin deficiency resulting in hyperglycemia (11-55 mmol/L), dehydration, and electrolyte abnormalities
- history and physical exam – often young, type 1 DM, may be first presentation of undiagnosed DM (may occur in small percentage of type 2 DM patients)
  - early symptoms: polyuria, polydipsia, malaise, nocturia, weight loss
  - late signs and symptoms
    - anorexia, nausea, vomiting, dyspnea (often due to acidosis), fatigue
    - abdominal pain
    - drowsiness, stupor, coma
    - Kussmaul’s respiration
    - fruity acetone breath
- investigations
  - CBC, glucose, electrolytes, BUN/Cr, Ca²⁺, Mg²⁺, PO₄³⁻, urine glucose and ketones
  - ABG
  - ECG (MI possible precipitant; electrolyte disturbances may predispose to dysrhythmia)
- management
  - rehydration
    - bolus of NS, then high rate NS infusion (beware of overhydration and cerebral edema, especially in pediatric patients)
    - beware of a pseudohyperonatremia due to hyperglycemia (add 3 Na⁺ per 10 glucose over 5.5 mmol/L)
  - potassium
    - essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K⁺ <3.5 mmol/L)
  - use cardiac monitoring if potassium levels normal or low
  - insulin
    - critical, as this is the only way to turn off gluconeogenesis/ketosis
    - do not give insulin if K⁺ <3.3 mmol/L
    - initial bolus of 5-10 U short-acting/regular insulin (or 0.2 U/kg) IV in adults (controversial – may just start with infusion)
    - followed by continuous infusion at 5-10 U (or 0.1 U/kg) per hour
    - add D5W to IV fluids when blood glucose <15 mmol/L to prevent hypoglycemia
  - bicarbonate is not given unless patient is at risk of death or shock (typically pH <7.0)

**Hyperosmolar Hyperglycemic State**
- state of extreme hyperglycemia (44-133.2 mmol/L) due to relative insulin deficiency, increased counter-regulatory hormones, gluconeogenesis, and dehydration (due to osmotic diuresis) in type 2 DM, high mortality (5-20%)
- history and physical exam
  - vitals, mental disturbances, coma, delirium, seizures
  - polyuria, N/V
  - find underlying cause
- investigations
  - CBC, electrolytes, Cr, BUN, glucose, Mg²⁺, PO₄³⁻, urine glucose and ketones, ABG
  - find underlying cause: ECG, CXR, blood and urine C&S
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O₂ and cardiac monitoring, frequent electrolyte and glucose monitoring
  - insulin is controversial
  - identify and treat precipitant if present (the 5 Is)

Figure 14. V/Q-based algorithm for suspected PE

<table>
<thead>
<tr>
<th>Normal V/Q scan and any clinical probability of PE</th>
<th>Low probability V/Q scan and low clinical probability of PE</th>
<th>High probability V/Q scan and high clinical probability of PE</th>
<th>All other combinations of V/Q scan results and clinical probability of PE</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE excluded</td>
<td>PE excluded</td>
<td>PE confirmed</td>
<td>Pulmonary angiogram or serial lower extremity venous US</td>
</tr>
</tbody>
</table>

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    - essential to avoid hypokalemia: replace KCl (20 mEq/L if adequate renal function and initial K⁺ <3.5 mmol/L)
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  - CBC, electrolytes, Cr, BUN, glucose, Mg²⁺, PO₄³⁻, urine glucose and ketones, ABG
  - find underlying cause: ECG, CXR, blood and urine C&S
- management
  - rehydration with IV NS (total water deficit estimated at average 100 cc/kg body weight)
  - O₂ and cardiac monitoring, frequent electrolyte and glucose monitoring
  - insulin is controversial
  - identify and treat precipitant if present (the 5 Is)
Hypoglycemia
- very common ED presentation
- history and physical exam
  - last meal, known DM, prior similar episodes, drug therapy, and compliance
  - liver/renal/endocrine/neoplastic disease
  - depression, alcohol or drug use
  - altered LOC with sympathomimetic response
- management
  - IV access and rapid blood glucose measurement
  - D50W 50 mL IV push, glucose PO if mental status permits
  - if IV access not possible, glucagon 1-2 mg IM, repeat x 1 in 10-20 min
  - O2, cardiac, frequent blood glucose monitoring
  - thiamine 100 mg IM
  - full meal as soon as mental status permits
  - if episode due to long-acting insulin, or sulfonylureas, watch for prolonged hypoglycemia due to long t1/2 (may require admission for monitoring)
  - search for cause (most often due to exogenous insulin, alcohol, or sulfonylureas)

Electrolyte Disturbances
- see Nephrology, NP7 and Endocrinology, E38

<table>
<thead>
<tr>
<th>Electrolyte Disturbance</th>
<th>Common Causes</th>
<th>Symptoms</th>
<th>Treatment</th>
<th>Special Considerations</th>
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<tbody>
<tr>
<td>Hypernatremia</td>
<td>Inadequate H2O intake (elderly/disabled) or inappropriate excretion of H2O</td>
<td>Lethargy, weakness, irritability, and edema; seizures and coma occur</td>
<td>Salt restrict and give free water</td>
<td>No more than 12 mmol/L in 24 h drop in Na⁺ (0.5 mmol/L/h) due to risk of cerebral edema, seizures, death</td>
</tr>
<tr>
<td></td>
<td>(dihydrates, Li, and DI)</td>
<td>with severe elevations of Na⁺ levels (&gt;158 mmol/L)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Hypovolemic (GI, renal, skin, blood fluid loss), euvoletic (SIADH/stress,</td>
<td>Neurologic symptoms 2nd to cerebral edema, headache, decreased LOC,</td>
<td>Water restrict/NPO; Seizure/Coma: 100cc 3% NaCl; Treat hypovolemia with RL and</td>
<td>Limit total rise to 8 mmol/L in 24 h (0.5 mmol/L/h maximum) as patients are at risk of central pontine myelinolysis</td>
</tr>
<tr>
<td></td>
<td>adrenal insufficiency, hypothyroid, diet/intake), hypervolemic (CHF, cirrhosis, nephrotic syndrome)</td>
<td>depressed reflexes; chronic milder than acute</td>
<td>furosemide</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Rhabdomyolysis, insulin deficiency, metabolic acidosis (e.g. acute renal</td>
<td>Nausea, palpitations, muscle stiffness, areflexia</td>
<td>Protect heart: calcium gluconate</td>
<td>High risk of dysrhythmia - ECG: peaked/narrow T wave, decreased P wave, prolonged PR interval, widening of QRS, AV block, VFib</td>
</tr>
<tr>
<td></td>
<td>failure, missed dialysis)</td>
<td></td>
<td>Shift K⁺ into cells: Insulin, NaHCO₃, salbutamol</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Remove K⁺: Fluids+furosemide, dialysis</td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Metabolic alkalosis (e.g. diarrhea), insulin, diuretics, anorexia, salbutamol</td>
<td>N/V, fatigue, muscle cramps, constipation</td>
<td>K-Dur®, K⁺ sparing diuretics, IV solutions with 20-40 mEq/L KCl over 3-4 h</td>
<td>ECG: U waves most important, flattened/inverted T waves, prolonged QT, depressed ST May need to restore Mg²⁺</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercalcemia</td>
<td>Hyper-PTH and malignancy account for ~90% of cases</td>
<td>Multisystem including CVS, GI (glands), renal (stones), rheumatological, MSK (bones), psychiatric (meas)</td>
<td>Isotonic saline+furosemide if hypercalcemic Biphosphonates, dialysis, chelation (EDTA or oral PO₄³⁻)</td>
<td>Patients with more severe or symptomatic hypercalcemia are usually dehydrated and require saline hydration as initial therapy</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>Iatrogenic, low Mg²⁺, liver dysfunction, 1st hypo-PTH</td>
<td>Laryngospasm, hypertonia, paresthesia, tetany, Chvostek’s and Trousseau’s sign</td>
<td>Acute (ionized Ca²⁺ &lt;0.7 mM) requires immediate treatment: IV calcium gluconate 1-2 g in 10-20 min followed by slow infusion</td>
<td>Prolonged QT interval can arise, leading to dysrhythmia as can upper airway obstruction</td>
</tr>
</tbody>
</table>

Hypertensive Emergencies

Hypertensive Emergency (Hypertensive Crisis)

Etiology
- essential HTN, emotional exertion, pain, use of sympathomimetic drugs (cocaine, amphetamine, etc.), MAOI use with ingestion of tyramine-containing food (cheese, red wine, etc.), pheochromocytoma, pregnancy

Presentation
- elevation of systolic and diastolic BP (irrespective of BP) with acute end-organ damage (CNS, renal, CVS, retinal)
Table 21. Signs and Symptoms of Hypertensive Emergencies

<table>
<thead>
<tr>
<th>Complication</th>
<th>CNS</th>
<th>Retinal</th>
<th>Renal</th>
<th>Cardiac</th>
<th>Gastrointestinal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/TIA, headache, altered mental status, seizures, hemorrhage</td>
<td>Vision change, hemorrhage, exudates, papilledema</td>
<td>Nocturia, elevated Cr, proteinuria, hematuria, oliguria</td>
<td>Ischemia/angina, infarct, dissection (back pain), CHF</td>
<td>N/V, abdominal pain, elevated liver enzymes</td>
<td></td>
</tr>
</tbody>
</table>

Table 22. Commonly Used Agents for the Treatment of Hypertensive Crisis

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Onset of Action</th>
<th>Duration of Action</th>
<th>Adverse Effects*</th>
<th>Special Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Nitroprusside</td>
<td>0.25-10 µg/kg/min</td>
<td>Immediate</td>
<td>3-5 min</td>
<td>N/V, muscle twitching, sweating, cyanide intoxication, coronary steal syndrome</td>
<td>Most hypertensive emergencies (especially CHF, aortic dissection) Use in combination with β-blockers (e.g. esmolol) in aortic dissection Caution with high ICP and azotemia</td>
</tr>
<tr>
<td>Nicardipine (CCB)</td>
<td>2 mg IV bolus, then 4 mg/kg/h IV</td>
<td>15-30 min</td>
<td>40 min</td>
<td>Tachycardia, headache, flushing, local phlebitis (e.g. encephalopathy, RF, eclampsia, sympathetic crisis)</td>
<td>Most hypertensive emergencies Caution with acute CHF</td>
</tr>
<tr>
<td>Fenoldopam Mesylate</td>
<td>0.05-0.1 µg/kg/min/min</td>
<td>&lt;5 min</td>
<td>8-10 min</td>
<td>Tachycardia, headache, nausea, flushing (e.g. acute RF)</td>
<td>Most hypertensive emergencies Caution with glaucoma</td>
</tr>
<tr>
<td>Enalapril (ACEI)</td>
<td>0.625-1.25 mg IV q6h</td>
<td>15-30 min</td>
<td>12-24 h</td>
<td>Theoretical fall in pressure in high renin states not seen in studies</td>
<td>Acute LV failure Avoid in acute MI, pregnancy, acute RF</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>5-20 µg/min IV</td>
<td>1-2 min</td>
<td>3-5 min</td>
<td>Hypotension, bradycardia, headache, lightheadedness, dizziness</td>
<td>MI/pulmonary edema</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>5-10 mg IV/IM q20min (max 20 mg)</td>
<td>5-20 min</td>
<td>2-6 h</td>
<td>Dizziness, drowsiness, headache, tachycardia, Na + retention</td>
<td>Eclampsia</td>
</tr>
</tbody>
</table>

Investigations
- CBC, electrolytes, BUN, Cr, U/A
- peripheral blood smear: to detect microangiopathic hemolytic anemia
- CXR: if SOB or chest pain
- ECG, troponins, CK: if chest pain
- CT head: if neurological findings or severe headache
- toxicology screen if sympathomimetic overdose suspected

Management
- in general, the strategy for management is to gradually and progressively reduce BP in 24-48 h
  - lower BP by 25% over the initial 60 min by initiating antihypertensive therapy (usually nitroprusside and labetalol)
  - if preeclampsia, immediately consult OB/GYN (see Obstetrics, OB25)
  - establish arterial line; transfer to ICU for further reduction in BP under monitored setting
  - in case of ischemic stroke: do not rapidly reduce BP, maintain BP >150/100 for 5 d
  - in case of aortic dissection: rapid reduction of sBP to 110-120 STAT (do not resuscitate with IV fluids)
  - in case of excessive catecholamines: avoid β-blockers (except labetalol)
  - in case of ACS: address ischemia initially, then BP

Hypertensive Urgency
- definition: severely elevated BP (usually sBP >180, dBP >115) with no evidence of end-organ damage
  - most commonly due to non-adherence with medications
  - treatment: initiate/adjust antihypertensive therapy, monitor in ED (up to 6 h) and discharge with follow up for 48-72 h
  - goal: differentiate hypertensive emergencies from hypertensive urgencies

HELLP Syndrome (seen only in preeclampsia/eclampsia)
- Hemolytic anemia
- Elevated Liver enzymes
- Low Platelet count

Catecholamine-Induced Hypertensive Emergencies
- Avoid use of non-selective β-blockers as they inhibit β-mediated vasodilation and leave α-adrenergic vasoconstriction unopposed

With CNS manifestations of severe HTN, it is often difficult to differentiate causal relationships (i.e. HTN could be secondary to a cerebral event with an associated Cushing reflex)
### Myocardial Infarction

- see [Cardiology and Cardiac Surgery], C28

**Management**
- early recognition of ACS on history and ECG
- immediate stabilization
  - ABCs, O₂, IV access, cardiac monitors
  - treat sustained ventricular arrhythmia as per ACLS
  - benzodiazepines for cocaine-related ACS
  - nitroglycerin 0.3 mg SL q5min x 3 for CHF, HTN, or pain; IV if persistent symptoms (contraindicated if hemodynamic compromise or phosphodiesterase inhibitor use)
  - previously, morphine used if unresponsive to nitroglycerin; however, it may impair activity of new antiplatelet agents
  - ASA 162-325 mg chewed and swallowed or if unable, per rectum
  - choice of anticoagulation (unfractionated heparin, LMWH, or fondaparinux) and additional antiplatelet therapy (clopidogrel, ticagrelor, or plasugrel) depends on STEMI vs. NSTEMI and reperfusion strategy
  - early cardiology consult and reperfusion therapy
    - UA/NSTEMI: early coronary angiography recommended if high TIMI risk score
    - STEMI: primary percutaneous coronary intervention (within 90 min) preferred; thrombolytics if unavailable within 120 min of medical contact, symptoms <12 hr and no contraindications
  - β-blocker if no signs of CHF, hemodynamic compromise, bradycardia or severe reactive airway disease
  - atorvastatin 80 mg to stabilize plaques

### Sepsis

- see [Infectious Diseases], ID22 and [Respirology], R33

**Management**
- early recognition of sepsis and investigations to locate source of infection
- identify severe sepsis with lactate or evidence of tissue hypoperfusion
- treatment priorities
  - ABCs, monitors and lines
  - aggressive fluid resuscitation; consider ventilatory and intropic support
  - cultures, then early empiric appropriate antibiotics - consider broad spectrum and atypical coverage
  - source control - e.g. remove infected Foley or surgery for ischemic gut
  - monitor adequate resuscitation with vital signs, inferior vena cava on U/S, and serial lactates
**Stroke and TIA**

- see Neurology, N50

**Definitions**
- Stroke: sudden loss of brain function due to ischemia (80%) or hemorrhage (20%) with persistence of symptoms >24 hr or neuroimaging evidence
- TIA: transient episode of neurologic dysfunction from focal ischemia without acute infarction typically lasting <1 h, but defined as <24 h

**Presentation**

**Table 23. Signs and Symptoms of Stroke**

<table>
<thead>
<tr>
<th>Signs/ Symptoms</th>
<th>General</th>
<th>Language/ Threat</th>
<th>Vision</th>
<th>Coordination</th>
<th>Motor</th>
<th>Sensation</th>
<th>Reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased LOC, changed mental status, confusion, neglect</td>
<td>Dysphagia, aphasia, swallowing difficulty</td>
<td>Diplopia, eye deviation, asymmetric pupils, visual field defect</td>
<td>Ataxia, intention tremor, lack of coordination</td>
<td>Increased tone, loss of power, spasticity</td>
<td>Loss of sensation</td>
<td>Hyper-reflexia, clonus</td>
<td></td>
</tr>
</tbody>
</table>

- patients with hemorrhagic stroke can present with sudden onset thunderclap headache that is usually described as “worst headache of life”
- stroke mimics: seizure, migraine, hypoglycemia, Todd’s paresis, peripheral nerve injury, Bell’s palsy, tumour, syncope

**Table 24. Stroke Syndromes**

<table>
<thead>
<tr>
<th>Region of Stroke</th>
<th>Stroke Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Cerebral Artery</td>
<td>Primarily frontal lobe function affected, altered mental status, impaired judgment, contralateral lower extremity weakness and hypoaesthesia, gait apraxia</td>
</tr>
<tr>
<td>Middle Cerebral Artery</td>
<td>Contralateral hemiparesis (arm and face weakness &gt; leg weakness) and hypothesia, ipsilateral hemianopsia, gaze preference to side of lesion ± agnosia, receptive/expressive aphasia</td>
</tr>
<tr>
<td>Posterior Cerebral Artery</td>
<td>Affects vision and thought, homonymous hemianopsia, cortical blindness, visual agnosia, altered mental status, impaired memory</td>
</tr>
<tr>
<td>Vertebralbasilar Artery</td>
<td>Wide variety of cranial nerve, cerebellar, and brainstem deficits: vertigo, nystagmus, diplopia, visual field deficits, dysphagia, dysarthria, facial hypothesia, syncope, ataxia</td>
</tr>
</tbody>
</table>

**Investigations**
- CBC, electrolytes, blood glucose, coagulation studies ± cardiac biomarkers ± toxicology screen
- non-contrast CT head: look for hemorrhage, ischemia
- ECG ± echocardiogram: rule out AFib, acute MI as source of emboli
- other imaging: carotid Dopplers, CTA, MRA as indicated

**Management**
- ABCs; intubation with RSI if GCS ≤8, rapidly decreasing GCS, or inadequate airway protection reflexes
- thrombolysis: immediate assessment for eligibility; need acute onset, <4.5 h from drug administration time AND compatible physical findings AND normal CT with no bleed
- elevating head of bed if risk of elevated ICP, aspiration, or worsening cardiopulmonary status
- NPO, IV ± cardiac monitoring
- judge fluid rate carefully to avoid overhydration (cerebral edema) as well as underhydration (underperfusion of the ischemic penumbra)
- BP control: only treat severe HTN (sBP >200, dBP >120, mean arterial BP >140) or HTN associated with hemorrhagic stroke transformation, cardiac ischemia, aortic dissection, or renal damage; use IV nitropresoride or labetalol
- glycemic control: keep fasting glucose <6.5 in acute phase (5 d)
- cerebral edema control: hyperventilation, mannitol to decrease ICP if necessary
- consult neurosurgery, neurology, medicine as indicated

**Medications**
- acute ischemic stroke: thrombolytics (rt-PA, e.g. alteplase) if within 4.5 h of symptom onset with no evidence of hemorrhage on CT scan
- antplatelet agents: prevent recurrent stroke or stroke after TIs, e.g. Aspirin® (1st line); clopidogrel, Aggrenox® (2nd line)
- anticoagulation: DVT prophylaxis if immobile; treat AFib if present
- follow-up for consideration of carotid endarterectomy, cardiovascular risk optimization
Otolaryngological Presentations and Emergencies

- see Otolaryngology, OT6
- ear associated symptoms: otalgia, aural fullness, otorrhea, hearing loss, tinnitus, vertigo, pruritis, fever
- risk factors: Q-tip use, hearing aids, headphones, occupational noise exposure

Dizziness and Vertigo

- distinguish four types of dizziness: vertigo (“room spinning”), lightheadedness (“disconnected from environment”), presyncope (“almost blacking out”), dysequilibrium (“unstable, off-balance”)
- broad differential and diverse management (see Family Medicine, FM26; Otolaryngology, OT6, OT12)
- consider medication adverse effects

Otalgia (see Otolaryngology, OT6)

- differential
  - infections: acute otitis externa, acute otitis media, otitis media with effusion, mastoiditis, myringitis, malignant otitis in diabetics, herpes simplex/zoster, auricular cellulitis, external canal abscess, dental disease
  - others: trauma, temporomandibular joint dysfunction, neoplasm, foreign body, cerumen impactions, trigeminal neuralgia, granulomatosis with polyangiitis
- observe for otorrhea, palpation of outer ear/mastoid, otoscope to see bulging erythematous tympanic membrane, perforation
- C&S of ear canal discharge, if present
- CT head if suspicion of mastoiditis, malignant otitis externa
- antibiotics/antifungals/antivirals for respective infections

Hearing Loss (see Otolaryngology, OT7)

- differentiate conductive versus sensorineural hearing loss
- rule out sudden sensorineural hearing loss (SNHL), a medical emergency requiring high dose steroids and urgent referral
- in elderly, unilateral tinnitus or SNHL is acoustic neuroma until proven otherwise
- consider audiogram and referral or follow-up with family physician

Epistaxis

- see Otolaryngology, OT27
- 90% of nosebleeds stem from the anterior nasal septum (at Kiesselbach’s plexus located in Little’s area)
- can be life-threatening

Etiology

- most commonly caused by trauma (digital, blunt, foreign bodies)
- other causes: barometric changes, nasal dryness, chemicals (cocaine, Otrivin*), or systemic disease (coagulopathies, HTN, etc.)

Investigations

- blood work: CBC, PT/PTT (as indicated)
- imaging: X-ray, CT as needed

Treatment

- aim is to localize bleeding and achieve hemostasis
- first-aid: ABCs, clear clots by blowing nose or suctioning, lean forward, pinch cartilaginous portion of nose for 20 min twice
- assess blood loss: vitals, IV NS, cross match 2 units pRBC if significant
- if first aid measures fail twice, proceed to packing
- apply an anterior pack
  - clear nose of any clots
  - apply topical anesthesia/vasoconstrictors (lidocaine with epinephrine, cocaine, or soaked pledgets)
  - insert either a traditional Vaseline® gauze pack or a commercial nasal tampon or balloon
  - if bleeding stops, arrange follow-up in 48-72 h for reassessment and pack removal
  - if packing both nares, prophylactic anti-staphylococcal antibiotics to prevent sinusitis or toxic shock syndrome
  - if bleeding is controlled with anterior pressure, cautery with silver nitrate can be performed if the site of bleeding is identified (one side of septum only because if both are cauterized this can lead to septal perforation)

Complications of Nasal Packing

- Hypoxemia
- Toxic-shock syndrome
- Aspiration
- Pharyngeal fibrosis/stenosis
- Alar/septal necrosis

Thrombocytopenic patients – use resorbable packs to avoid risk of re-bleeding caused by pulling out the removable pack
• if suspect posterior bleed or anterior packing does not provide hemostasis, consult ENT for posterior packing and further evaluation
  ▪ posterior packing (ENT consult)
  ▪ posterior packing requires monitoring because can cause significant vagal response and posterior bleeding source can lead to significant blood loss

Disposition
• discharge: discharged upon stabilization and appropriate follow-up; educate patients about prevention (e.g. humidifiers, saline spray, topical ointments, avoiding irritants, managing HTN)
• admission: severe cases of refractory bleeding

Gynecologic/Urologic Emergencies

Vaginal Bleeding
• see Gynecology, GY6 and Obstetrics, OB14, OB45

Etiology
• pregnant patient
  ▪ 1st/2nd trimester pregnancy: ectopic pregnancy, abortion (threatened, incomplete, complete, missed, inevitable, septic), molar pregnancy, implantation bleeding, friable cervix (most common cause)
  ▪ 2nd/3rd trimester pregnancy: placenta previa, placental abruption, premature rupture of membranes, preterm labour
  ▪ other: trauma, bleeding cervical polyp, passing of mucous plug
• postpartum
• postpartum hemorrhage, uterine inversion, retained placental tissue, endometritis
• non-pregnant patients
  ▪ dysfunctional uterine bleeding, uterine fibroids, pelvic tumours, trauma, endometriosis, PID, exogenous hormones

History
• characterize bleeding (frequency, duration, number of pads/tampons, cyclicity)
• pain, if present (OPQRSTU)
• menstrual history, sexual history, STI history, syncope/pre-syncope
• details of pregnancy, including gush of fluid and fetal movement (>20 wk)

Physical Exam
• ABC (especially noting postural BP/HR and mucous membrane)
• abdominal examination (peritoneal signs, tenderness, distension, mass)
• speculum examination (NOT IF 2nd/3rd trimester bleeding; perform only when placenta previa is ruled out with U/S)
  ▪ look for active bleeding, trauma/anomaly, and cervical dilatation
  ▪ use sterile speculum if pregnant
• bimanual examination (cervical tenderness, size of uterus, cervical length/dilatation)
• sterile gloves if pregnant

Investigations
• β-hCG test for all patients with childbearing potential
• CBC, blood and Rh type, quantitative β-hCG, PTT, INR
• type and cross if significant blood loss
• transvaginal U/S (rule out ectopic pregnancy and spontaneous abortion)
• abdominal U/S (rule out placenta previa and fetal demise)
• postpartum
• U/S for retained products
• β-hCG if concerned about retained tissue

Management
• ABCs
• pulse oximeter and cardiac monitors if unstable
• Rh immune globulin (Rhogam®) for vaginal bleeding in pregnancy and Rh-negative mother
• 1st/2nd trimester pregnancy
  ▪ ectopic pregnancy: definitive treatment with surgery or methotrexate
  ▪ intrauterine pregnancy, no concerns of coexistent ectopic: discharge patient with obstetrics follow-up
• U/S indeterminate or β-hCG >1,000-2,000 IU: further workup and/or gynecology consult
• abortions: if complete, discharge if stable; for all others, acquire gynecology consult

Vaginal bleeding can be life-threatening
Always start with ABC’s and ensure your patient is stable

Need β-hCG ≥1,200 to see intrauterine changes on transvaginal U/S

An ectopic pregnancy can be ruled out by confirming an intrauterine pregnancy by bedside U/S unless the patient is using IVF

Vaginal bleeding (and its underlying causes) can be a very distressing event for patients; ensure appropriate support is provided
• 2nd/3rd trimester pregnancy
  - placenta previa or placental abruption: obstetrics consult for possible admission
• postpartum
  - manage ABCs: start 2 large bore IV rapid infusion, type and cross 4 units of blood, consult OB/GYN immediately
• non-pregnant
  - dysfunctional uterine bleeding (prolonged or heavy flow ± breakthrough bleeding and without ovulation, a diagnosis of exclusion)
    - <35-40 yr of age: Provera® 10 mg PO OD x 10 d, warn patient of a withdrawal bleed, discharge if stable
    - if unstable, admit for IV hormonal therapy, possible D&C
    - >35-40 yr of age: uterine sampling necessary prior to initiation of hormonal treatment to rule out endometrial cancer, U/S for any masses felt on exam
    - tranexamic acid (Cyklokapron®) to stabilize clots
  - structural abnormalities: fibroids or uterine tumours may require excision for diagnosis/treatment, U/S for workup of other pelvic masses, Pap smear/biopsy for cervical lesions

Disposition
• decision to admit or discharge should be based on the stability of the patient, as well as the nature of the underlying cause; consult gynecology for admitted patients
• if patient can be safely discharged, ensure follow-up with family physician or gynecologist
• instruct patient to return to ED for increased bleeding, presyncope

### Pregnant Patient in the ED

#### Table 25. Complications of Pregnancy

<table>
<thead>
<tr>
<th>Trimester</th>
<th>Fetal</th>
<th>Maternal</th>
</tr>
</thead>
</table>
| First 1-12 wk | Pregnancy failure  
• Spontaneous abortion  
• Fetal demise  
• Gestational trophoblastic disease | Ectopic pregnancy  
Anemia  
Hyperemesis gravidarum  
UTI/pyelonephritis |
| Second 13-27 wk | Disorders of fetal growth  
• IUGR  
• Oligo/polyhydramnios | Gestational DM  
Rh incompatibility  
UTI/pyelonephritis |
| Third 28-41 wk | Vasa previa | Preterm labour/PPROM  
Preeclampsia/eclampsia  
Placenta previa  
Placental abruption  
Uterine rupture  
DVT |

### Nephrolithiasis (Renal Colic)

- see Urology, U17

#### Epidemiology and Risk Factors
- 10% of population (twice as common in males)
- recurrence 50% at 5 yr
- peak incidence 30-50 yr of age
- 75% of stones <5 mm pass spontaneously within 2 wk, larger stones may require consultation

#### Clinical Features
- urinary obstruction → upstream distention of ureter or collecting system → severe colicky pain
- may complain of pain at flank, groin, testes, or tip of penis
- writhing, never comfortable, N/V, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
- occasionally symptoms of trigonal irritation (frequency, urgency)
- fever, chills, rigors in secondary pyelonephritis
- peritoneal findings/anterior abdominal tenderness usually absent

#### Differential Diagnosis of Renal Colic
- acute ureteric obstruction
- acute abdomen: biliary, bowel, pancreas, AAA
- gynaecological: ectopic pregnancy, torsion/rupture of ovarian cyst
- pyelonephritis (fever, chills, pyuria, vomiting)
- radiculitis (L1): herpes zoster, nerve root compression
Investigations
- screening
- CBC → elevated WBC in presence of fever suggests infection
- electrolytes, Cr, BUN → to assess renal function
- U/A: WBCs, RBCs, crystals, C&S
- imaging
- non-contrast spiral CT is the study of choice
- abdominal U/S may demonstrate stone or hydronephrosis (consider in females of childbearing age)
- AXR will identify large radioopaque stones (calcium, struvite, and cystine stones) but may miss smaller stones, uric acid stones, or stones overlying bony structures; consider as an initial investigation in patients who have a history of radioopaque stones and similar episodes of acute flank pain (CT necessary if film is negative)
- strain all urine ← stone analysis

Management
- analgesics: NSAIDs (usually ketorolac [Toradol®], preferable over opioids), antiemetics, IV fluids
- urology consult may be indicated, especially if stone >5 mm, or if patient has signs of obstruction or infection
- α-blocker (e.g. tamsulosin) helpful to increase stone passage in select cases

Disposition
- most patients can be discharged
- ensure patient is stable, has adequate analgesia, and is able to tolerate oral medications
- may advise hydration and limitation of protein, sodium, oxalate, and alcohol intake

Ophthalmologic Emergencies
- see Ophthalmology, OP5

History and Physical Exam
- patient may complain of pain, tearing, itching, redness, photophobia, foreign body sensation, trauma
- mechanism of foreign body insertion – if high velocity injury suspected (welding, metal grinding, metal striking metal), must obtain orbital X-rays, U/S, or CT scan to exclude presence of intraocular metallic foreign body
- visual acuity in both eyes, pupils, extraocular structures, fundoscopy, tonometry, slit lamp exam

Management of Ophthalmologic Foreign Body
- copious irrigation with saline for any foreign body
- remove foreign body under slit lamp exam with cotton swab or sterile needle
- antibiotic drops qid until healed
- patching may not improve healing or comfort – do not patch contact lens wearers
- limit use of topical anesthetic to examination only
- consider tetanus prophylaxis
- ophthalmology consult if globe penetration suspected

Table 26. Differential Diagnosis of Red Eye in the Emergency Department

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Serious Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light sensitivity</td>
<td>Iritis, keratitis, abrasion, ulcer</td>
</tr>
<tr>
<td>Unilateral</td>
<td>Above + herpes simplex, acute angle closure glaucoma</td>
</tr>
<tr>
<td>Significant pain</td>
<td>Above + scleritis</td>
</tr>
<tr>
<td>White spot on cornea</td>
<td>Corneal ulcer</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>All of the above</td>
</tr>
<tr>
<td>Non-reactive pupil</td>
<td>Acute glaucoma, iritis</td>
</tr>
<tr>
<td>Copious discharge</td>
<td>Gonococcal conjunctivitis</td>
</tr>
<tr>
<td>Blurred vision</td>
<td>All of the above</td>
</tr>
</tbody>
</table>

Visual acuity is the “vital sign” of the eyes and should ALWAYS be assessed in both eyes when a patient presents to the ER with an ophthalmologic complaint
### Table 27. Select Ophthalmologic Emergencies

<table>
<thead>
<tr>
<th>Condition</th>
<th>Signs and Symptoms</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Angle Closure</strong></td>
<td>Unilateral red, painful eye</td>
<td>Ophthalmology consult for laser iridotomy</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>Decreased visual acuity, halos around lights</td>
<td>Topical β-blockers, α-adrenergics, and cholinergics</td>
</tr>
<tr>
<td></td>
<td>Fixed, mid-dilated pupil</td>
<td>Systemic carbonic anhydrase inhibitors and hyperosmotic agents</td>
</tr>
<tr>
<td></td>
<td>N/V</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marked increase in IOP (&gt;40 mmHg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shallow anterior chamber ± cells</td>
<td></td>
</tr>
<tr>
<td><strong>Chemical Burn</strong></td>
<td>Known exposure to acids or alkali (worse)</td>
<td>Irrigate at site of accident</td>
</tr>
<tr>
<td></td>
<td>Pain, decreased visual acuity</td>
<td>IV NS drip in ED with eyelid retracted</td>
</tr>
<tr>
<td></td>
<td>Vascularization or defects of cornea</td>
<td>Swab fornices</td>
</tr>
<tr>
<td></td>
<td>Iris and lens damage</td>
<td>Cycloplegic drops</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Topical antibiotics and patching</td>
</tr>
<tr>
<td><strong>Orbital Cellulitis</strong></td>
<td>Red, painful eye, decreased visual acuity</td>
<td>Admission, ophthalmology consult</td>
</tr>
<tr>
<td></td>
<td>Headache, fever</td>
<td>Blood cultures, orbital CT</td>
</tr>
<tr>
<td></td>
<td>Lid erythema, edema, and difficulty opening eye</td>
<td>IV antibiotics (ceftriaxone + vancomycin)</td>
</tr>
<tr>
<td></td>
<td>Conjunctival injection and chemosis</td>
<td>Drainage of abscess</td>
</tr>
<tr>
<td><strong>Retinal Artery Occlusion</strong></td>
<td>Sudden, painless, monocular vision loss</td>
<td>Restore blood flow &lt;2 h</td>
</tr>
<tr>
<td></td>
<td>RAPD</td>
<td>Massage globe</td>
</tr>
<tr>
<td></td>
<td>Cherry red spot and retinal pallor on fundoscopy</td>
<td>Decrease IOP (topical β-blockers, inhaled O₂/CO₂ mix, IV Diamox®, IV mannitol, drain aqueous fluid)</td>
</tr>
<tr>
<td><strong>Retinal Artery Detachment</strong></td>
<td>Flashes of light, floaters, and curtains of blackness/ peripheral vision loss</td>
<td>Ophthalmology consult for scleral buckle/ pneumatic retinopexy</td>
</tr>
<tr>
<td></td>
<td>Painless</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Loss of red reflex, decreased IOP</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Detached areas are gray ± RAPD</td>
<td></td>
</tr>
</tbody>
</table>

### Dermatologic Emergencies

#### Life-Threatening Dermatoses

**Rash Characteristics**

**A. Diffuse Rashes**

- SSSS
  - caused by an exotoxin from infecting strain of coagulase-positive *S. aureus*
  - mostly occurs in children
  - prodrome: fever, irritability, malaise, and skin tenderness
  - sudden onset of diffuse erythema: skin is red, warm, and very tender
  - flaccid bullae that are difficult to see, then desquamate in large sheets
  - Nikolsky’s sign: gentle lateral stroking of skin causes epidermis to separate

- TEN (>30% of BSA)
  - see Dermatology, D23
  - caused by drugs (e.g. phenytoin, sulfas, penicillins, and NSAIDs), bone marrow transplantation, and blood product transfusions
  - usually occurs in adults
  - diffuse erythema followed by necrosis
  - severe mucous membrane blistering
  - entire epidermis desquamation
  - high mortality (>50%)

- TSS
  - see Infectious Diseases, ID23
  - caused by superantigen from *S. aureus* or GAS activating T-cell and cytokines
  - patient often presents with onset of shock and multi-organ failure, fever
  - diffuse erythematous macular rash
  - at least 3 organ systems involved: CNS, respiratory, GI, muscular, mucous membranes, renal, liver, hematologic, and skin (necrotizing fasciitis, gangrene)

- vesicobullous lesions

- EM
  - see Dermatology, D30
  - immunologic reaction to herpes simplex
  - viral prodrome 1-14 d before rash
  - "target lesion": central grey bulla or wheal surrounded by concentric rings of erythema and normal skin
SJS (<10% of BSA)
- see Dermatology, D23
- related to drugs such as antiepileptics and biologic agents (e.g. infliximab)
- EM with constitutional symptoms and mucous membrane involvement (milder mucous membrane involvement than TEN)

B. Discrete Lesions
- pyoderma gangrenosum
  - often associated with immunocompromised patients (HIV, leukemia, or lymphoma) with Gram-negative sepsis
  - often occurs in arms, hands, feet, or perineal region
  - usually begins as painless macule/vesicle → pustule/bulla on red/blue base → sloughing, leaving a gangrenous ulcer
- disseminated gonococcal infection
  - see Dermatology, D33
  - fever, skin lesions (pustules/vesicles on erythematous base ~5 mm in diameter), arthritis (joint swelling and tenderness), and septic arthritis (in larger joints, such as knees, ankles, and elbows)
  - most commonly in gonococcus positive women during menstruation or pregnancy
  - skin lesions usually appear in extremities and resolve quickly (<7 d)
- meningococcemia
  - flu-like symptoms of headache, myalgia, N/V
  - petechial, macular, or maculopapular lesions with gray vesicular centres
  - usually a few millimeters in size, but may become confluent and hemorrhagic
  - usually appear in extremities, but may appear anywhere
  - look for signs of meningeal irritation: Brudzinski, Kernig, nuchal rigidity, jolt accentuation

History and Physical Exam
- determine onset, course, and location of skin lesions
- fever, joint pain
- associated symptoms: CNS, respiratory, GU, GI, renal, liver, mucous membranes
- medication history
- vitals

Investigations
- immediate consultation if patient unstable
- CBC, electrolytes, Cr, AST, ALT, ALP, blood culture, skin biopsy, serum immunoglobulin levels (serum IgE)

Management
- general: judicious IV fluids and electrolyte control, consider vaspressors if hypotensive, prevention of infection
- determine if admission and consult needed: dermatology or infectious diseases
- specific management is determined by etiology
  - SSSS, TSS, DGI, and meningococcemia
    - IV antibiotics
  - EM, SJS, and TEN
    - stop precipitating medication
    - fluids
    - symptomatic treatment: antihistamines, antacids, topical corticosteroids, systemic corticosteroids (controversial), prophylactic oral acyclovir, consider IVIG
  - TEN: debride necrotic tissue

Disposition
- most cases will require urgent care and hospitalization
- TEN: early transfer to burn centre improves outcome
Environmental Injuries

Heat Exhaustion and Heat Stroke

- **predisposing factors:** young persons who overexert themselves, older adults who cannot dissipate heat at rest (e.g. using anticholinergic drugs such as antihistamines or TCAs), and patients with schizophrenia who are using anticholinergic or antiepileptic medications

**Heat Exhaustion**
- clinical features relate to loss of circulating volume caused by exposure to heat stress
- “water depletion”: heat exhaustion occurs if lost fluid not adequately replaced
- “salt depletion”: heat exhaustion occurs when losses replaced with hypotonic fluid

**Heat Stroke**
- life-threatening emergency resulting from failure of normal compensatory heat-shedding mechanisms
- divided into classical and exertional subtypes
- if patient does not respond relatively quickly to cooling treatments, consider other possible etiologies of hyperpyrexia (e.g. meningitis, thyroid storm, anticholinergic poisoning, delirium tremens, other infections)

<table>
<thead>
<tr>
<th>Table 28. Heat Exhaustion vs. Heat Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Features</strong></td>
</tr>
<tr>
<td>- Non-specific malaise, headache, fatigue</td>
</tr>
<tr>
<td>- Body temp &lt;40.5°C (usually normal)</td>
</tr>
<tr>
<td>- No coma or seizures</td>
</tr>
<tr>
<td>- Dehydration (↑ HR, orthostatic hypotension)</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>- Rest in a cool environment</td>
</tr>
<tr>
<td>- IV NS if orthostatic hypotension; otherwise replace losses slowly PO</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Hypothermia and Cold Injuries

**HYPOTHERMIA**
- predisposing factors: extremes of age, lack of housing, drug overdose, EtOH ingestion, trauma (incapacitating), cold water immersion, outdoor sports
- treatment based on re-warming and supporting cardiorespiratory function
- complications: coagulopathy, acidosis, ventricular dysrhythmias (VFib), asystole, volume and electrolyte depletion
- labs: CBC, electrolytes, ABG, serum glucose, Cr/BUN, Mg²⁺, Ca²⁺, amylase, coagulation profile
- imaging: CXR (aspiration pneumonia, pulmonary edema are common)
- monitors: ECG, rectal thermometer, Foley catheter, NG tube, monitor metabolic status frequently

<table>
<thead>
<tr>
<th>Table 29. Classification of Hypothermia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class</strong></td>
</tr>
<tr>
<td>Mild</td>
</tr>
<tr>
<td>Moderate</td>
</tr>
<tr>
<td>Severe</td>
</tr>
</tbody>
</table>
Re-warming Options
- gentle fluid and electrolyte replacement in all (due to cold diuresis)
- Passive External Re-warming
  - suitable for most stable patients with core temperature >32.2°C
  - involves covering patient with insulating blanket; body generates heat and re-warms through metabolic process, shivering
- Active External Re-warming
  - involves use of warming blankets
  - beware of “afterdrop” phenomenon
  - safer when done in conjunction with active core re-warming
- Active Core Re-warming
  - generally for patients with core temperature <32.2°C, and/or with cardiovascular instability
  - avoids “afterdrop” seen with AER alone
  - re-warm core by using
    - warmed humidified oxygen, IV fluids
    - peritoneal dialysis with warm fluids
    - gastric/colonic/pleural irrigation with warm fluids
    - external circulation (cardiopulmonary bypass machine) is most effective and fastest

Approach to Cardiac Arrest in the Hypothermic Patient
- do all procedures gently or may precipitate VFib
- check pulse and rhythm for at least 1 min; may have profound bradycardia
- if any pulse at all (even very slow) do NOT do CPR
- if in VFib try to defibrillate up to maximum 3 shocks if core temperature <30°C
- intubate if required, ventilate with warmed, humidified O₂
- medications (vasopressors, antidysrhythmics) may not be effective at low temperatures
  - controversial; may try one dose
- focus of treatment is re-warming

FROSTBITE
Classification
- ice crystals form between cells
- classified according to depth – similar to burns (1st to 3rd degree)
  - 1st degree
    - symptoms: initial paresthesia, pruritus
    - signs: erythema, edema, hyperemia, no blisters
  - 2nd degree
    - symptoms: numbness
    - signs: blistering (clear), erythema, edema
  - 3rd degree
    - symptoms: pain, burning, throbbing (on thawing); may be painless if severe
    - signs: hemorrhagic blisters, skin necrosis, edema, no movement

Management
- treat for hypothermia: O₂, IV fluids, maintenance of body warmth
- remove wet and constrictive clothing
- immerse in 40–42°C agitated water for 10-30 min (very painful; administer adequate analgesia)
- clean injured area and leave it open to air
- consider aspiration/debridement of blisters (controversial)
- debride skin
- tetanus prophylaxis
- consider penicillin G as frost bite injury has high risk of infection
- surgical intervention may be required to release restrictive eschars
- never allow a thawed area to re-chill/freeze

Burns
- see Plastic Surgery, PL17

Physical Exam
- burn size
  - rule of nines; does not include 1st degree burns
- burn depth
  - superficial (1st degree): epidermis only (e.g. sunburn), painful and tender to palpation
  - superficial partial thickness (2nd degree): extends to epidermis and superficial dermis, blister formation occurs, very painful
  - deep partial thickness (2nd degree): involves hair follicles, sebaceous glands; skin is blistered, exposed dermis is white to yellow, absent sensation

Figure 15. Rule of 9s for total BSA
full thickness (3rd degree): epidermis and all dermal layers; skin is pale, insensate, and charred or leathery
- deep (4th degree): involvement of fat, muscle, even bone

Management
- remove noxious agent/stop burning process
- establish airway if needed (indicated with burns >40% BSA or smoke inhalation injury)
- resuscitation for 2nd and 3rd degree burns (after initiation of 2 large bore IVs)
- fluid boluses if unstable
  - Parkland Formula: Ringer's lactate 4 cc/kg/%BSA burned; give half in first 8 h, half in next 16 h; maintenance fluids are also required if patient cannot tolerate PO hydration
  - urine output is best measure of resuscitation, should be 40-50 cc/h or 0.5 cc/kg/h; avoid diuretics
- pain relief: continuous morphine infusion with breakthrough bolus
- investigations: CBC, electrolytes, U/A, CXR, ECG, ABG, carboxyhemoglobin
- burn wound care: prevent infection, clean/debride with mild soap and water, sterile dressings
- escharotomy or fasciotomy for circumferential burns (chest, extremities)
- topical antibiotics, systemic antibiotics infrequently indicated
- tetanus prophylaxis if burn is deeper than superficial dermis

Disposition
- admit
  - 2nd degree burns >10% BSA, or any significant 3rd degree burns
  - 2nd degree burns on face, hands, feet, perineum, or across major joints
  - electrical, chemical burns, and inhalation injury
  - burn victims with underlying medical problems or immunosuppressed patients

Inhalation Injury

Etiology
- CO or cyanide poisoning
- direct thermal injury: limited to upper airway
- smoke causes bronchospasm and edema from particulate matter and toxic inhalants (tissue asphyxiates, pulmonary irritants, systemic toxins)

History and Physical Exam
- risk factors: closed space fires, period of unconsciousness, noxious chemicals involved
- cherry red skin (unreliable, usually post-mortem finding)
- singed nasal hairs, soot on oral/nasal membranes, sooty sputum
- hoarseness, stridor, dyspnea
- decreased LOC, confusion
- PO2 normal but O2 saturation low suggests CO poisoning

Investigations
- measure carboxyhemoglobin levels, co-oximetry
- ABG
- CXR ± bronchoscopy

Management
- CO poisoning: 100% O2 ± hyperbaric O2 (controversial)
- direct thermal injury: humidified oxygen, early intubation, pulmonary toilet, bronchodilators

Bites

MAMMALIAN BITES
- see Plastic Surgery, PL10

History
- time and circumstances of bite, symptoms, allergies, tetanus immunization status, comorbid conditions, rabies risks, HIV/hepatitis risk (human bite)
- high morbidity associated with clenched fist injuries, “fight bites”

Physical Exam
- assess type of wound: abrasion, laceration, puncture, crush injury
- assess for direct tissue damage: skin, bone, tendon, neurovascular status
Investigations
- if bony injury or infection suspected, check for fracture and gas in tissue with x-rays
- get skull films in children with scalp bite wounds ± CT to rule out cranial perforation

Initial Management
- wound cleansing and copious irrigation as soon as possible
- irrigate/debride puncture wounds if feasible, but not if sealed or very small openings; avoid hydrodissection along tissue planes
- debridement is important in crush injuries to reduce infection and optimize cosmetic and functional repair
- culture wound if signs of infection (erythema, necrosis, or pus); obtain anaerobic cultures if wound foul smelling, necrotizing, or abscess; notify lab that sample is from bite wound

Prophylactic Antibiotics
- types of infections resulting from bites: cellulitis, lymphangitis, abscesses, tenosynovitis, osteomyelitis, septic arthritis, sepsis, endocarditis, meningitis
- a 3-5 d course of antibiotics is recommended for all bite wounds to the hand and should be considered in other bites if any high-risk factors present (efficacy not proven)
- dog and cat bites (pathogens: Pasteurella multocida, S. aureus, S. viridans)
  - 10-50% of cat bites, 5% of dog bites become infected
  - 1st line: amoxicillin + clavulanic acid
- human bites (pathogens: Eikenella corrodens, S. aureus, S. viridans, oral anaerobes)
  - 1st line: amoxicillin + clavulanic acid
- rabies (see Infectious Diseases, ID21)
  - reservoirs: warm-blooded animals except rodents, lagomorphs (e.g. rabbits)
  - post-exposure vaccine is effective; treatment depends on local prevalence
- suturing
  - vascular structures (i.e. face and scalp) are less likely to become infected, therefore consider suturing
  - allow avascular structures (i.e. pretibial regions, hands, and feet) to heal by secondary intention
  - tetanus immunization if >10 yr or incomplete primary series

SNAKE BITES
- history, physical exam, investigations, and initial management similar to mammalian bites
- additional management issues
  - snake bites are rarely fatal, but proper precautions must be taken
  - supportive management, observe for compartment syndrome, analgesia, tetanus prophylaxis
  - contact Provincial Poison Information Centre for consultation
  - for the Massasauga rattlesnake ONLY: if no signs of local tissue damage AND an INR is normal at 6 h after the bite, the patient may be discharged
  - there is NO evidence that constriction bands are helpful AND can be harmful
  - if envenomation present, administer antivenom as directed by local Poison Information Centre

INSECT BITES
- bee stings
  - 5 types of reactions to stings (local, large local, systemic, toxic, unusual)
  - history and physical exam key to diagnosis; no lab test will confirm
  - investigations: CBC, electrolytes, BUN, Cr, glucose, ABGs, ECG
  - ABC management, epinephrine 0.1 mg IV over 5 min if shock, antihistamines, cimetidine 300 mg IV/IM/PO, steroids, β-agonists for SOB/wheezing 3 mg in 5 mL NS via nebulizer, local site management
  - West Nile virus (see Infectious Diseases, ID24)

Near Drowning
- most common in children <4 yr and teenagers
- causes lung damage, hypoxemia, and may lead to hypoxic encephalopathy
- must also assess for shock, C-spine injuries, hypothermia, and scuba-related injuries (barotrauma, air emboli, lung re-expansion injury)
- complications: volume shifts, electrolyte abnormalities, hemolysis, rhabdomyolysis, renal, DIC

Physical Exam
- ABCs, vitals: watch closely for hypotension
- respiratory: rales (ARDS, pulmonary edema), decreased breath sounds (pneumothorax)
- CVs: murmurs, dysrhythmias, JVP (CHE, pneumothorax)
- H&N: assess for C-spine injuries
- neurological: GCS or AVPU, pupils, focal deficits
Investigations
- labs: CBC, electrolytes, ABGs, Cr, BUN, INR, PTT, U/A (drug screen, myoglobin)
- imaging: CXR (pulmonary edema, pneumothorax) ± C-spine imaging
- ECG

Management
- ABCs, treat for trauma, shock, hypothermia
- cardiac and O2 monitors, IV access
- intensive respiratory care
  - ventilator assistance if decreased respirations, pCO₂ >50 mmHg, or pO₂ <60 mmHg on maximum O₂
  - may require intubation for airway protection, ventilation, pulmonary toilet
  - high flow O₂/CPAP/BiPAP may be adequate but some may need mechanical ventilation with positive end-expiratory pressure
- dysrhythmias: usually respond to corrections of hypoxemia, hypothermia, and acidosis
- vomiting: very common, NG suction to avoid aspiration
- convulsions: usually respond to O₂; if not, diazepam 5-10 mg IV slowly
- bronchospasm: bronchodilators
- bacterial pneumonia: prophylactic antibiotics not necessary unless contaminated water or hot tub (Pseudomonas)
- always initiate CPR in drowning-induced cardiac arrest even if patient hypothermic; continue CPR until patient is fully rewarmed

Disposition
- non-significant submersion: discharge after short observation
- significant submersion (even if asymptomatic): long period of observation (24 h) as pulmonary edema may appear late
- CNS symptoms or hypoxemia: admit
- severe hypoxemia, decreased LOC: ICU

Toxicology

“ABCD₃EFG” of Toxicology
- basic axiom of care is symptomatic and supportive treatment
- address underlying problem only once patient is stable

- Airway (consider stabilizing the C-spine)
- Breathing
- Circulation
- Drugs
  - ACLS as necessary to resuscitate the patient
  - universal antidotes
- Draw bloods
- Decontamination (decrease absorption)
- Expose (look for specific toxidromes)/Examine the patient
- Full vitals, ECG monitor, Foley, X-rays
- Give specific antidotes and treatments

- reassess
- call Poison Information Centre
- obtain corroborative history from family, bystanders

D1 – Universal Antidotes
- treatments that will not harm patients and may be essential

Dextrose (glucose)
- give to any patient presenting with altered LOC
- measure blood glucose prior to glucose administration if possible
- adults: 0.5-1.0 g/kg (1-2 mL/kg) IV of D50W
- children: 0.25 g/kg (2-4 mL/kg) IV of D25W

Oxygen
- do not deprive a hypoxic patient of oxygen no matter what the antecedent medical history (i.e. even COPD with CO₂ retention)
- if depression of hypoxic drive, intubate and ventilate
- exception: paraquat or diquat (herbicides) inhalation or ingestion (oxygen radicals increase morbidity)
Naloxone (central μ-receptor competitive antagonist, shorter t1/2 than naltrexone)
- antidote for opioids: administration is both diagnostic and therapeutic (1 min onset of action)
- used for the undifferentiated comatose patient
- loading dose
  - adults
    - response to naloxone can be drastic, so stepwise delivery of initial 2 mg bolus is recommended
    - draw up 2 mg to deliver IV/IM/SL/SC or via ETT (ETT dose = 2-2.5x IV dose)
      - 1st dose 0.4 mg
      - if no response, deliver second dose 0.6 mg
      - if still no response, deliver remaining 1 mg
  - child
    - 0.01 mg/kg initial bolus IV/IO/ETT
    - 0.1 mg/kg if no response and opioid still suspected to max of 10 mg
- maintenance dose
  - may be required because half-life of naloxone (30-80 min) is much shorter than many opioids
  - hourly infusion rate at 2/3 of initial dose that allowed patient to be roused

Thiamine (Vitamin B1)
- 100 mg IV/IM with IV/PO glucose to all patients
- given to prevent/treat Wernicke's encephalopathy
- a necessary cofactor for glucose metabolism (may worsen Wernicke's encephalopathy if glucose given before thiamine), but do not delay glucose if thiamine unavailable
- must assume all undifferentiated comatose patients are at risk

D2 – Draw Bloods
- essential tests
  - CBC, electrolytes, BUN/Cr, glucose, INR/PTT, osmolality
  - ABGs, measure O2 sat
  - ASA, acetylsalicylic acid, EtOH levels
- potentially useful tests
  - drug levels – this is NOT a serum drug screen
    - Ca²⁺, Mg²⁺, PO₄³⁻
  - protein, albumin, lactate, ketones, liver enzymes, CK – depending on drug and clinical presentation

Serum Drug Levels
- treat the patient, not the drug level
- negative toxicology screen does not rule out a toxic ingestion – signifies only that the specific drugs tested were not detectable in the specimen
- specific drugs available on general screen vary by institution; check before ordering
- urine screens also available (qualitative only)

Table 30. Toxic Gaps (see Nephrology, NP15)

<table>
<thead>
<tr>
<th>METABOLIC ACIDOSIS</th>
<th>Increased AG: “MUDPILES CAT” (↑ = toxic)</th>
<th>Decreased AG: Electrolyte imbalance (increased Na⁺/K⁺/Mg²⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methanol†</td>
<td>Diabetic ketoacidosis/Starvation ketoacidosis</td>
<td>Hypoalbuminemia (50% fall in albumin ~5.5 mmol/L decrease in the AG)</td>
</tr>
<tr>
<td>Uremia</td>
<td>Phenformin*/Paraldehyde*</td>
<td>Lithium, bromide elevation</td>
</tr>
<tr>
<td>Diabetic ketoacidosis/Starvation ketoacidosis</td>
<td>Isoniazid, Irubuprofen</td>
<td>Paraproteins (multiple myeloma)</td>
</tr>
<tr>
<td>Lactic acid (anything that causes seizures or shock)</td>
<td>Ethylene glycol*</td>
<td>Normal AG: High K⁺: pyelonephritis, obstructive nephropathy, renal tubular acidosis IV, TPN</td>
</tr>
<tr>
<td>Ethylene glycol*</td>
<td>Salicylates*</td>
<td>Low K⁺: small bowel losses, acetazolamide, renal tubular acidosis I, II</td>
</tr>
<tr>
<td>Cyanide, CO²†</td>
<td>Alcoholic ketoacidosis</td>
<td>Increased POG: “MAE DIE” (if it ends in “-ol”, it will likely increase the POG)</td>
</tr>
<tr>
<td>Toluene, theophylline*</td>
<td>Methanol†</td>
<td>Methanol</td>
</tr>
<tr>
<td>Methanol†</td>
<td>Acetone</td>
<td>Acetone</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Ethanol</td>
<td>Ethanol</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td>Diuretics (glycerol, mannitol, sorbitol)</td>
<td>Isopropanol</td>
</tr>
<tr>
<td>Ethylene glycol</td>
<td></td>
<td>Ethylene glycol</td>
</tr>
</tbody>
</table>

Note: normal POG does not rule out toxic alcohol; only an elevated gap is helpful

Increased O₂ saturation gap
- Carboxyhemoglobin
- Methemoglobin
- Sulphmethemoglobin

Urine drug screen is costly and generally not helpful in the ED management of the poisoned patient

Administration of naloxone can cause opioid withdrawal in chronic users:
- Minor withdrawal may present as lacrimation, rhinorrhea, diaphoresis, yawning, piloerection, HTN, and tachycardia
- Severe withdrawal may present as hot and cold flashes, arthralgias, myalgias, N/V, and abdominal cramps

Populations at Risk for Thiamine Deficiency
- Alcoholics
- Anorexics
- Hyperemesis of pregnancy
- Malnutrition states

Anion Gap
- Na⁺ – Cl⁻ – HCO₃⁻
- Normal AG ≤ 12 mM/L
Table 31. Use of the Clinical Laboratory in the Initial Diagnosis of Poisoning

<table>
<thead>
<tr>
<th>Test</th>
<th>Finding</th>
<th>Selected Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABG</td>
<td>Hypoventilation (↑ pCO2)</td>
<td>CNS depressants (opioids, sedative-hypnotic agents, phenothiazines, ETOH)</td>
</tr>
<tr>
<td></td>
<td>Hyperventilation (↓ pCO2)</td>
<td>Salicylates, CO, other asphyxiants</td>
</tr>
<tr>
<td>Electrolytes</td>
<td>↑ AG metabolic acidosis</td>
<td>“MUDPILES CAT”: see Table 26</td>
</tr>
<tr>
<td></td>
<td>Hyperkalemia</td>
<td>Digitalis glycosides, fluoride, potassium</td>
</tr>
<tr>
<td></td>
<td>Hypokalemia</td>
<td>Theophylline, caffeine, β-adrenergic agents, soluble barium salts, diuretics, insulin</td>
</tr>
<tr>
<td>Glucose</td>
<td>Hypoglycemia</td>
<td>Oral hypoglycemic agents, insulin, ETOH, ASA</td>
</tr>
<tr>
<td>Osmolality and Osmolar Gap</td>
<td>Elevated osmolar gap</td>
<td>“MAE DIE”: see Table 30</td>
</tr>
<tr>
<td>ECG</td>
<td>Wide QRS complex</td>
<td>TCAs, quinidine, other class Ia and Ic antidyssrhythmic agents</td>
</tr>
<tr>
<td></td>
<td>Prolonged QT interval</td>
<td>Terfenadine, astemizole, antipsychotics</td>
</tr>
<tr>
<td></td>
<td>Atioventricular block</td>
<td>Ca2+ antagonists, digitalis glycosides, phenylpropanolamine</td>
</tr>
<tr>
<td>Abdominal X-Ray</td>
<td>Radioopaque pills or objects</td>
<td>“CHIPS”: Calcium, Chloral hydrate, CCl4, Heavy metals, Iron, Potassium, Enteric coated Salicylates, and some foreign bodies</td>
</tr>
<tr>
<td>Serum Acetaminophen</td>
<td>Elevated level (&gt;140 mg/L or 1,000 µmol/L 4 h after ingestion)</td>
<td>May be only sign of acetaminophen poisoning</td>
</tr>
</tbody>
</table>

D3 – Decontamination and Enhanced Elimination

Ocular Decontamination
- saline irrigation to neutralize pH; alkali exposure requires ophthalmology consult

Dermal Decontamination (Wear Protective Gear)
- remove clothing, brush off toxic agents, irrigate all external surfaces

Gastrointestinal Decontamination
- single dose activated charcoal
  - adsorption of drug/toxin to activated charcoal prevents availability
  - contraindications: caustics, small bowel obstruction, perforation
  - dose: 10 g/g drug ingested or 1g/kg body weight
  - odourless, tasteless, prepared as slurry with H2O
- whole bowel irrigation
  - 500 mL/h (child) to 2000 mL/h (adult) of polyethylene glycol solution by mouth until clear effluent per rectum
  - start slow (500 mL in an adult) and aim to increase rate hourly as tolerated
  - indications
    - awake, alert, can be nursed upright OR intubated and airway protected
    - delayed release product
    - drug/toxin not bound to charcoal
    - drug packages (if any evidence of breakage → emergency surgery)
  - recent toxin ingestion
- contraindications
  - evidence of ileus, perforation, or obstruction
  - surgical removal in extreme cases
    - indicated for drugs that are toxic, form concretions, or cannot be removed by conventional means
  - no evidence for the routine use of cathartics (i.e. ipecac)

Urine Alkalization
- may be used for: ASA, methotrexate, phenobarbital, chloropropamide
- weakly acidic substances can be trapped in alkali urine (pH >7.5) to increase elimination

Multidose Activated Charcoal
- may be used for: carbamazepine, phenobarbital, quinine, theophylline
- for toxins which undergo enterohepatic recirculation
- removes drug that has already been absorbed by drawing it back into GI tract
- various regimens: 12.5 g (1/4 bottle) PO q1h or 25 g (1/2 bottle) PO q2h until non-toxic

Hemodialysis
- indications/criteria for hemodialysis
  - toxins that have high water solubility, low protein binding, low molecular weight, adequate concentration gradient, small volume of distribution, or rapid plasma equilibration
  - removal of toxin will lead to clinical improvement
• advantage is shown over other modes of therapy
• predicted that drug or metabolite will have toxic effects
• impairment of normal routes of elimination (cardiac, renal, or hepatic)
• clinical deterioration despite maximal medical support
• useful for the following toxins
  - methanol
  - ethylene glycol
  - salicylates
• others include theophylline, carbamazepine, valproate, methotruxate

### E – Expose and Examine the Patient

- vital signs (including temperature), skin (needle tracks, colour), mucous membranes, pupils, odours, and CNS
- head-to-toe survey including
  - C-spine
  - signs of trauma, seizures (incontinence, “tongue biting”, etc.), infection (meningismus), or chronic alcohol/drug abuse (track marks, nasal septum erosion)
- mental status

Table 32. Specific Toxidromes

<table>
<thead>
<tr>
<th>Toxidrome</th>
<th>Overdose Signs and Symptoms</th>
<th>Examples of Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>“Hot as a hare”</td>
<td>Antidepressants (e.g. TCAs)</td>
</tr>
<tr>
<td>Dilated pupils</td>
<td>“Blind as a bat”</td>
<td>Cyclobenzaprine (Flexeril®)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>“Dry as a bone”</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Vasodilation</td>
<td>“Red as a beet”</td>
<td>Antihistamines (e.g. diphenhydramine)</td>
</tr>
<tr>
<td>Agitation/hallucinations</td>
<td>“Mad as a hatter”</td>
<td>Antiparkinsonians</td>
</tr>
<tr>
<td>Ileus</td>
<td>“The bowel and bladder lose their tone and the heart goes on alone”</td>
<td>Antipsychotics</td>
</tr>
<tr>
<td>Urinary retention</td>
<td></td>
<td>Belladonna alkaloids (e.g. atropine)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholinergic</td>
<td>“DUMBELS”</td>
<td></td>
</tr>
<tr>
<td>Diaphoresis, Diarrhea, Decreased BP</td>
<td>Natural plants: mushrooms, trumpet flower</td>
<td></td>
</tr>
<tr>
<td>Urination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Miosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bronchospasm, Bronchorrhea, Bradycardia</td>
<td>Anticholinesterases: physostigmine</td>
<td></td>
</tr>
<tr>
<td>Emesis, Excitation of skeletal muscle</td>
<td>Insecticides (organophosphates, carbamates)</td>
<td></td>
</tr>
<tr>
<td>Lacrimation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salivation, Seizures</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysphonia, dysphagia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigidly and tremor</td>
<td></td>
<td>Major tranquillizers</td>
</tr>
<tr>
<td>Motor restlessness, crawling sensation (akathisia)</td>
<td>Antipsychotics</td>
<td></td>
</tr>
<tr>
<td>Constant movements (dyskinesia)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystonia (muscle spasms, laryngospasm, trismus, oculogyric crisis, torticollis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemoglobin Derangements</td>
<td>Increased respiratory rate</td>
<td>CO poisoning (carboxyhemoglobin)</td>
</tr>
<tr>
<td></td>
<td>Decreased LOC</td>
<td>Drug ingestion (methemoglobin, sulfmethemoglobin)</td>
</tr>
<tr>
<td></td>
<td>Seizures</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cyanosis unresponsive to O₂</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Lactic acidosis</td>
<td></td>
</tr>
<tr>
<td>Opioid, Sedative/ Hypnotic, EtOH</td>
<td>Hypothermia</td>
<td>EtOH</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td></td>
<td>Respiratory depression</td>
<td>Opioids (morphine, heroin, fentanyl, etc.)</td>
</tr>
<tr>
<td></td>
<td>Dilated or constricted pupils (pinpoint in opioid)</td>
<td>Barbiturates</td>
</tr>
<tr>
<td></td>
<td>CNS depression</td>
<td>Gamma hydroxybutyrate</td>
</tr>
<tr>
<td>Sympathomimetic</td>
<td>Increased temperature</td>
<td>Amphetamines, caffeine, cocaine, LSD, phencyclidine</td>
</tr>
<tr>
<td></td>
<td>CNS excitation (including seizures)</td>
<td>Ephedrine and other decongestants</td>
</tr>
<tr>
<td></td>
<td>Tachycardia, HTN</td>
<td>Thyroid hormone</td>
</tr>
<tr>
<td></td>
<td>N/V</td>
<td>Sedative or EtOH withdrawal</td>
</tr>
<tr>
<td></td>
<td>Diaphoresis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dilated pupils</td>
<td></td>
</tr>
<tr>
<td>Serotonin Syndrome</td>
<td>Mental status changes, autonomic hyperactivity, neuromuscular abnormalities, hyperthermia, diarrhea, HTN</td>
<td>MАОI, TCA, SSRI, opiate analgesics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cough medicine, weight reduction medications</td>
</tr>
</tbody>
</table>

Note: ASA poisoning and hypoglycemia mimic sympathomimetic toxidrome

### F – Full Vitals, ECG Monitor, Foley, X-Rays
## Urine Alkalization Specific Antidotest and Treatments

- **Urine Alkalization Treatment for ASA Overdose**
  - urine pH >7.5
  - fluid resuscitate first, then 3 amps NaHCO₃/L of D5W at 1.5x maintenance
  - add 20-40 mEq/L KCl if patient is able to urinate

### Table 33. Protocol for Warfarin Overdose

<table>
<thead>
<tr>
<th>INR</th>
<th>Management: Consider Prothrombin Complex Concentrate (Octaplex®, Beriplex®) for any elevated INR, AND either life-threatening bleeding, or a plan for the patient to undergo a surgical procedure within the next 6 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5.0</td>
<td>Cessation of warfarin administration, observation, serial INR/PT</td>
</tr>
<tr>
<td>5.1–9.0</td>
<td>If no risk factors for bleeding, hold warfarin x 1-2 d and reduce maintenance dose OR Vitamin K 1-2 mg PO if patient at increased risk of bleeding</td>
</tr>
<tr>
<td>9.1–20.0</td>
<td>Hold warfarin, vitamin K 2-4 mg PO, serial INR/PT, additional vitamin K if necessary</td>
</tr>
<tr>
<td>&gt;20.0</td>
<td>Hold warfarin, vitamin K 10 mg IV over 10 min, increase vitamin K dosing (q4h) if needed</td>
</tr>
</tbody>
</table>

### Table 34. Specific Antidotest and Treatments for Common Toxins*

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Treatment</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Decontaminate (activated charcoal)</td>
<td>Often clinically silent; evidence of liver/renal damage delayed &gt;24 h</td>
</tr>
<tr>
<td></td>
<td>N-acetylcysteine</td>
<td>Toxic dose &gt; 200 mg/kg (&gt; 7.5 g adult)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor drug level 4 h post-ingestion; also liver enzymes, INR, PTT, BUN, Cr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoglycemia, metabolic acidosis, encephalopathy → poor prognosis</td>
</tr>
<tr>
<td>Acute Dystonic Reaction</td>
<td>Benztropine: 1-2 mg IM/IV then 2 mg PO x 3 d OR Diphenhydramine: 1-2 mg/kg IV, then 25 mg PO qd x 3 d</td>
<td>Benztropine (Cogentin®) has euphoric effect and potential for abuse</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td>Decontaminate (activated charcoal)</td>
<td>Special antidotes available; consult Poison Information Centre</td>
</tr>
<tr>
<td>ASA</td>
<td>Decontaminate (activated charcoal)</td>
<td>Monitor serum pH and drug levels closely</td>
</tr>
<tr>
<td></td>
<td>Alkalize urine; want urine pH &gt; 7.5</td>
<td>Monitor K⁺ level; may require supplement for urine alkalization</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hemodialysis may be needed if intractable metabolic acidosis, very high levels, or end-organ damage (i.e. unable to diurese)</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Decontaminate (activated charcoal)</td>
<td>Flumazenil</td>
</tr>
<tr>
<td></td>
<td>Supportive care</td>
<td></td>
</tr>
<tr>
<td>β-blockers</td>
<td>Decontaminate (activated charcoal)</td>
<td>Consult Poison Information Centre</td>
</tr>
<tr>
<td></td>
<td>Consider high dose insulin eglycemia therapy</td>
<td>Some dialyzable, some intralipids</td>
</tr>
<tr>
<td>Calcium Channel Blockers</td>
<td>Decontaminate (activated charcoal)</td>
<td>Order ECG, electrolytes (especially Ca²⁺, Mg²⁺, Na⁺, K⁺)</td>
</tr>
<tr>
<td></td>
<td>CaCl₂: 1-4 g of 10% solution IV if hypotensive</td>
<td>Other: high dose insulin eglycemia isotopes or intralipids</td>
</tr>
<tr>
<td>Cocaine</td>
<td>Decontaminate (activated charcoal) if oral Aggressive supportive care</td>
<td>β-blockers are contraindicated in acute cocaine toxicity</td>
</tr>
<tr>
<td>CO Poisoning</td>
<td>See Inhalation Injury, ER47</td>
<td>Intralipid for life-threatening symptoms</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Hydroxocobalamin</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>Decontaminate (activated charcoal)</td>
<td>Use for life-threatening dysrhythmias unresponsive to conventional therapy, 6 h serum digoxin &gt;12 nmol/L, initial K⁺ &gt; 5 mmol/L, ingestion &gt;10 mg (adult)/&gt;4 mg (child)</td>
</tr>
<tr>
<td></td>
<td>Digoxin-specific Ab fragments</td>
<td>Common dysrhythmias include VFib, VTach, and conduction blocks</td>
</tr>
<tr>
<td></td>
<td>10-20 vials IV if acute; 3-6 if chronic</td>
<td>Some dialyzable, some intralipids</td>
</tr>
<tr>
<td></td>
<td>1 vial (40 mg) neutralizes 0.5 mg of toxin</td>
<td>Some dialyzable, some intralipids</td>
</tr>
<tr>
<td>Ethanol</td>
<td>Thiamine 100 mg IM/V</td>
<td>Hypoglycemia very common in children</td>
</tr>
<tr>
<td></td>
<td>Manage airway and circulatory support</td>
<td>Mouthwash = 70% EtOH; perfumes and colognes = 40-60% EtOH</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Order serum EtOH level and glucose level; treat glucose level appropriately</td>
</tr>
<tr>
<td>Ethylene Glycol/ Methanol</td>
<td>Fomepizole (4-methylpyrazole)</td>
<td>CBC, electrolytes, glucose, ethanol level</td>
</tr>
<tr>
<td></td>
<td>15 mg/kg IV load over 30 min, then 10 mg/kg q2h OR Ethanol (10%) 10 mL/kg over 30 min, then 1.5 mL/h</td>
<td>Consider hemodialysis</td>
</tr>
<tr>
<td>Heparin</td>
<td>Protamine sulfate 25-50 mg IV</td>
<td>For unfractionated heparin overdose only</td>
</tr>
<tr>
<td>Insulin IM/SC/ Oral Hypoglycemic</td>
<td>Glucose IV/PO/NG tube</td>
<td>Glyburide carries highest risk of hypoglycemia among oral agents</td>
</tr>
<tr>
<td></td>
<td>Glucagon: 1-2 mg IM (if no access to glucose)</td>
<td>Consider octreotide for oral hypoglycemics (50-100 μg SC q6h) in these cases; consult local Poison Information Centre</td>
</tr>
<tr>
<td>MDMA Opioids</td>
<td>Decontaminate (activated charcoal), supportive care</td>
<td>Monitor CK; treat rhabdomyolysis with high flow fluids: aggressive external cooling for hyperthermia</td>
</tr>
<tr>
<td>TCA</td>
<td>Flumazenil antidote contraindicated in combined TCA and benzodiazepine overdose</td>
<td>See Universal Antidotes, ER48</td>
</tr>
<tr>
<td></td>
<td>Also consider cardiac and hypotension support, seizure control</td>
<td>Consider local Poison Information Centre</td>
</tr>
<tr>
<td></td>
<td>NaHCO₃ bolus for wide QRS/seizures</td>
<td>Inotropic therapy (consult local Poison Information Centre)</td>
</tr>
</tbody>
</table>

* Call local Poison Information Centre for specific doses and treatment recommendations
Alcohol Related Emergencies

- see Psychiatry, PS24

Acute Intoxication
- slurred speech, CNS depression, disinhibition, lack of coordination
- nystagmus, diplopia, dysarthria, ataxia may progress to coma
- hypotension (peripheral vasodilation)
- if obtunded, rule out
  - head trauma/intracranial hemorrhage
  - associated depressants/street drugs, toxic alcohols
    - may also contribute to respiratory/cardiac depression
  - hypoglycemia (screen with bedside glucometer)
  - hepatic encephalopathy: confusion, altered LOC, coma
    - precipitating factors: GI bleed, infection, sedation, electrolyte abnormalities, protein meal
  - Wernicke's encephalopathy (ataxia, ophthalmoplegia, delirium)
  - post-ictal state, basilar stroke

Withdrawal
- beware of withdrawal signs
- treatment
  - diazepam 10-20 mg IV/PO or lorazepam 2-4 mg IV/PO q1h until calm
  - frequency of dosing may have to be increased depending on clinical response
  - may use CIWA protocol and give benzodiazepines as above until CIWA <10
  - thiamine 100 mg IM/IV then 50-100 mg/d
  - magnesium sulfate 4 g IV over 1-2 h (if hypomagnesemic)
  - admit patients with DT or multiple seizures

Table 35. Alcohol Withdrawal Signs

<table>
<thead>
<tr>
<th>Time Since Last Drink</th>
<th>Syndrome</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-8 h</td>
<td>Mild withdrawal</td>
<td>Generalized tremor, anxiety, agitation, but no delirium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Autonomic hyperactivity (situs tachycardia), insomnia, N/V</td>
</tr>
<tr>
<td>1-2 d</td>
<td>Alcoholic hallucinations</td>
<td>Visual (most common), auditory, and tactile hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vitals often normal</td>
</tr>
<tr>
<td>8 h-2 d</td>
<td>Withdrawal seizures</td>
<td>Typically brief generalized tonic-clonic seizures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May have several within a few hours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CT head if focal seizures have occurred</td>
</tr>
<tr>
<td>3-5 d</td>
<td>DT</td>
<td>5% of untreated withdrawal patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely confused state, fluctuating LOC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agitation, insomnia, hallucinations/delusions, tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tachycardia, hyperpyrexia, diaphoresis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High mortality rate</td>
</tr>
</tbody>
</table>

Cardiovascular Complications
- HTN
- cardiomyopathy; SOB, edema
- dysrhythmias (“holiday heart”)
- AFib (most common), atrial flutter, SVT, VTach (especially Torsades if hypomagnesemic/hypokalemic)

Metabolic Abnormalities
- alcoholic ketoacidosis
  - AG metabolic acidosis, urine ketones, low glucose, and normal osmolality
  - history of chronic alcohol intake with abrupt decrease/cessation
  - malnourished, abdominal pain with N/V
  - treatment: dextrose, thiamine (100 mg IM/IV prior to dextrose), volume repletion (with NS)
  - generally resolves in 12-24 h
- other alcohols
  - ethylene glycol → CNS, CVS, renal findings
  - methanol
    - early: lethargy, confusion
    - late: headache, visual changes, N/V, abdominal pain, tachypnea
  - both ethylene glycol and methanol produce severe metabolic acidosis with anion gap (as the alcohol is metabolized) and osmolar gap (initially after ingestion but before metabolism)
  - EtOH co-ingestion is protective
treatment
- urgent hemodialysis required
- fomepizole 15 mg/kg IV bolus OR EtOH 10% IV bolus and infusion to achieve blood level of 22 mmol/L (EtOH loading may be done PO)
- consider folic acid for methanol, and pyridoxine and thiamine for ethylene glycol – both help reduce conversion to active metabolites
- other abnormalities associated with alcohol: hypomagnesemia, hypophosphatemia, hypocalcemia, hypoglycemia, hypokalemia

Gastrointestinal Abnormalities
- gastritis
  - common cause of abdominal pain and GI bleed in chronic alcohol users
- pancreatitis
  - serum amylase very unreliable in patients with chronic pancreatitis, may need serum lipase
  - hemorrhagic form (15%) associated with increased mortality
  - fluid resuscitation very important
- hepatitis
  - AST/ALT ratio >2 suggests alcohol as the cause as well as elevated GGT with acute ingestion
- peritonitis/spontaneous bacterial peritonitis
  - leukocytosis, fever, generalized abdominal pain/tenderness
  - occasionally accompanies cirrhosis
  - paracentesis for diagnosis (common pathogens: E. coli, Klebsiella, Streptococcus)
- GI bleeds
  - most commonly gastritis or ulcers, even if patient known to have varices
  - consider Mallory-Weiss tear secondary to retching
  - often complicated by underlying coagulopathies
  - minor: treat with antacids
  - severe or recurrent: endoscopy

Disposition
- before patient leaves ED ensure stable vital signs, can walk unassisted, and fully oriented
- offer social services to find shelter or detox program
- ensure patient can obtain any medications prescribed and can complete any necessary follow-up

Approach to the Overdose Patient

History
- age, weight, underlying medical problems, medications
- substance and how much
- time and symptoms since exposure determines prognosis and need for decontamination
- route
- intention, suicidality

Physical Exam
- focus on: ABCs, LOC/GCS, vitals, pupils

Disposition from the Emergency Department
- methanol, ethylene glycol
  - delayed onset, admit and watch clinical and biochemical markers
- TCAs
  - prolonged/delayed cardiotoxicity warrants admission to monitored (ICU) bed
  - if asymptomatic and no clinical signs of intoxication: 6 h ED observation adequate with proper decontamination and no ECG abnormalities
  - sinus tachycardia alone (most common finding) with history of overdose warrants observation in ED
- hydrocarbons/smoke inhalation
  - pneumonitis may lag 6-8 h
  - consider observation for repeated clinical and radiographic examination
- ASA, acetaminophen
  - if borderline level, get second level 2-4 h after first
  - for ASA, must have at least 2 levels going down before discharge (3 levels minimum)
- oral hypoglycemics
  - admit all patients for minimum 24 h if hypoglycemic and 12 h after last octreotide dose
  - observe asymptomatic patient for at least 8 h

Psychiatric Consultation
- once patient medically cleared, arrange psychiatric intervention if required
- beware – suicidal ideation may not be expressed
Psychiatric Emergencies

Approach to Common Psychiatric Presentations

• see Psychiatry, PS2
• before seeing patient, ensure your own safety; have security/police available if necessary

History
• safety
  ▸ assess suicidality: suicidal ideation (SI), intent, plan, lethal means, and past attempts
  ▸ assess homicidality: homicidal ideation (HI), access to weapons, intended victim, and history of violence
  ▸ driving and children
  ▸ command hallucinations
  ▸ identify current stressors and coping strategies
• mood symptoms: manic, depressive
• anxiety: panic attacks, generalized anxiety, phobias, obsessive-compulsive disorder, post-traumatic stress disorder
• psychotic symptoms: delusions, hallucinations, disorganized speech, disorganized or catatonic behaviour, negative symptoms (affective flattening, alogia, avolition)
• substance use history: most recent use, amount, previous withdrawal reactions
• past psychiatric history, medications, adherence with medications
• medical history: obtain collateral if available

Physical Exam
• complete physical exam focusing on: vitals, neurological exam, signs of head trauma, signs of drug toxicity, signs of metabolic disorder
• mental status exam: general appearance, behavior, cooperation, speech, mood and affect, thought content and form, perceptual disturbances, cognition (including MMSE if indicated), judgment, insight, reliability

Investigations
• investigations vary with age, established psychiatric diagnosis vs. first presentation, history and physical suggestive of organic cause
• as indicated: blood glucose, urine and serum toxicology screen, pregnancy test, electrolytes, TSH, AST/ALT, bilirubin, serum Cr, BUN, osmolality
• blood levels of psychiatric medications
• CT head if suspect neurological etiology
• LP if indicated

Acute Psychosis

Differential Diagnosis
• primary psychotic disorder (e.g. schizophrenia)
• secondary to medical condition (e.g. delirium)
• drugs: substance intoxication or withdrawal, medications (e.g. steroids, anticholinergics)
• infectious (CNS)
• metabolic (hypoglycemic, hepatic, renal, thyroid)
• structural (hemorrhage, neoplasm)

Management
• violence prevention
  ▸ remain calm, empathic, and reassuring
  ▸ ensure safety of staff and patients, have extra staff and/or security on hand
  ▸ patients demonstrating escalating agitation or overt violent behavior may require physical restraint and/or chemical tranquillization
  ▸ treat agitation: whenever possible, offer medication to patients as opposed to administering with force (helps calm and engage patient)
    ▸ benzodiazepines: lorazepam 2 mg PO/IM/SL
    ▸ antipsychotics: olanzapine 5 mg PO, haloperidol 5 mg PO/IM
• treat underlying medical condition
• psychiatry or Crisis Intervention Team consult

Key Functions of Emergency Psychiatric Assessment
• Is the patient medically stable?
• Rule out medical cause
• Is psychiatric consult needed?
• Are there safety issues (SI, HI)?
• Is patient certifiable? (must demonstrate risk [present/past test] and apparent mental illness [future test])

Psychiatric Review of Systems
MOAPS
Mood
Organic
Anxiety
Psychosis
Safety
**Suicidal Patient**

**Epidemiology**
- attempted suicide F>M, completed suicide M>F
- second leading cause of death in people <24 yr

**Management**
- ensure patient safety: close observation, remove potentially dangerous objects from person and room
- assess thoughts (ideation), means, action (preparatory, practice attempts), previous attempts
- admit if there is evidence of intent and organized plan, access to lethal means, psychiatric disorder, intoxication (suicidal ideation may resolve with few days of abstinence)
- patient may require certification if unwilling to stay voluntarily
- do not start long-term medications in the ED
- psychiatry or Crisis Intervention Team consult

**Common Pediatric ED Presentations**

**Modified Glasgow Coma Score**

<table>
<thead>
<tr>
<th>Modified GCS for Infants</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Opening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 – spontaneously</td>
<td>5 – coos, babbles</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td>3 – to speech</td>
<td>4 – irritable cry</td>
<td>5 – withdraws to touch</td>
</tr>
<tr>
<td>2 – to pain</td>
<td>3 – cries to pain</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td>1 – no response</td>
<td>2 – moans to pain</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – decorticate extension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – no response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Modified GCS for Children &lt; 4 years</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eye Opening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 – spontaneously</td>
<td>5 – oriented, social, speaks, interacts</td>
<td>6 – normal, spontaneous movement</td>
</tr>
<tr>
<td>3 – to speech</td>
<td>4 – confused speech, disoriented, consolable</td>
<td>5 – localizes to pain</td>
</tr>
<tr>
<td>2 – to pain</td>
<td>3 – inappropriate words, not consolable/aware</td>
<td>4 – withdraws to pain</td>
</tr>
<tr>
<td>1 – no response</td>
<td>2 – incomprehensible, agitated, restless, not aware</td>
<td>3 – decorticate flexion</td>
</tr>
<tr>
<td></td>
<td>1 – no response</td>
<td>2 – decorticate extension</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 – no response</td>
</tr>
</tbody>
</table>

**Respiratory Distress**

- see Pediatrics, P74

**History and Physical Exam**
- infants not able to feed, older children not able to speak in full sentences
- anxious, irritable, lethargic – may indicate hypoxia
- tachypnea >60 (>40 if preschool age, >30 if school age), retractions, tracheal tug
  - see Pediatrics, P3 for age specific vital signs
- pulsus paradoxus
- wheezing, grunting, vomiting

<table>
<thead>
<tr>
<th>Table 37. Stridorous Upper Airway Diseases: Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Feature</strong></td>
</tr>
<tr>
<td>Age Range (yr)</td>
</tr>
<tr>
<td>Prodrome</td>
</tr>
<tr>
<td>Temperature</td>
</tr>
<tr>
<td>Radiography</td>
</tr>
<tr>
<td>Etiology</td>
</tr>
<tr>
<td>Barky Cough</td>
</tr>
<tr>
<td>Drooling</td>
</tr>
<tr>
<td>Appear Toxic</td>
</tr>
<tr>
<td>Intubation/ICU</td>
</tr>
<tr>
<td>Antibiotics</td>
</tr>
<tr>
<td>NOTE</td>
</tr>
</tbody>
</table>

¹Now rare with Hib vaccine in common use
Management

- croup (usually laryngotracheitis caused by parainfluenza viruses)
  - humidified O₂ should not be given (no evidence for efficacy)
  - racemic epinephrine q1h x 3 doses, observe for ‘rebound effects’
  - nebulized 1:1000 epinephrine (racemic has limited availability)
  - dexamethasone x 1 dose
  - consider bacterial tracheitis/epiglottitis if unresponsive to croup therapy

- bacterial tracheitis
  - start croup therapy, but may have poor response
  - usually require intubation, ENT consult, ICU
  - start antibiotics (e.g. cloxacillin), pending C&S

- epiglottitis
  - 4 Ds: drooling, dyspnea, dysphagia, dysphonia + tripod sitting
  - do not examine oropharynx or agitate patient
  - immediate anesthesia, ENT call – intubate
  - then IV fluids, antibiotics, blood cultures

- asthma
  - supplemental O₂ if saturation <90% or PaO₂ <60%
  - bronchodilator therapy: salbutamol (Ventolin®) 0.15 mg/kg by masks q20min x 3
  - add 250-500 µg ipratropium (Atrovent®) to first 3 doses salbutamol
  - give corticosteroid therapy as soon as possible after arrival (prednisolone 2 mg/kg, dexamethasone 0.3 mg/kg)
  - if critically ill, not responding to inhaled bronchodilators or steroids: give IV bolus, then infusion of MgSO₄
  - IV β₂-agonists if critically ill and not responding to above

Febrile Infant and Febrile Seizures

FEBRILE INFANT
- see Pediatrics, P53
  - for fever >38ºC without obvious focus
    - <28 d
      - admit
      - full septic workup (CBC and differential, blood C&S, urine C&S, LP ± stool C&S, CXR if indicated)
      - treat empirically with broad spectrum IV antibiotics
    - 28-90 d
      - as above unless infant meets Rochester criteria, investigate as indicated by history and physical
    - >90 d
      - toxic: admit, treat, full septic workup
      - non-toxic and no focus: investigate as indicated by history and physical

FEBRILE SEIZURES
- see Pediatrics, P84

Etiology

- children aged 6 mo-6 yr with fever or history of recent fever
- typical vs. atypical febrile seizures
- normal neurological exam afterward
- no evidence of intracranial infection or history of previous non-febrile seizures
- often positive family history of febrile seizures
- relatively well-looking after seizure

Investigations and Management

- if it is a febrile seizure: treat fever and look for source of fever
- if not a febrile seizure: treat seizure and look for source of seizure
  - note: may also have fever but may not meet criteria for febrile seizure
  - ± EEG (especially if first seizure), head U/S (if fontanelle open)

Table 38. Typical vs. Atypical Febrile Seizures

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration</td>
<td>&lt;15 min</td>
<td>&gt;15 min</td>
</tr>
<tr>
<td>Type of Seizure</td>
<td>Generalized</td>
<td>Focal features</td>
</tr>
<tr>
<td>Frequency</td>
<td>1 in 24 h</td>
<td>&gt;1 in 24 h</td>
</tr>
</tbody>
</table>
Abdominal Pain

- see Pediatrics, P39

History
- nature of pain, associated fever
- associated GI, GU symptoms
- anorexia, decreased fluid intake

Physical Exam
- HEENT, respiratory, abdominal exam including DRE, testicular/genital exam

Table 39. Differential Diagnosis of Abdominal Pain in Infants/Children/Adolescents

<table>
<thead>
<tr>
<th>Medical</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colic</td>
<td>Malrotation with volvulus</td>
</tr>
<tr>
<td>UTI</td>
<td>Hirschsprung’s disease</td>
</tr>
<tr>
<td>Constipation</td>
<td>Necrotizing enterocolitis</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Incarcerated hernia</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura</td>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>IBD</td>
<td>Appendicitis</td>
</tr>
<tr>
<td>Hemolytic uremic syndrome</td>
<td>Cholecystitis</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Strep throat</td>
<td>Testicular torsion</td>
</tr>
<tr>
<td>Sickle cell disease crisis</td>
<td>Ectopic pregnancy</td>
</tr>
<tr>
<td>DKA</td>
<td>Trauma</td>
</tr>
<tr>
<td>Functional</td>
<td>Pyloric stenosis</td>
</tr>
</tbody>
</table>

*Remember to keep an index of suspicion for child abuse

Common Infections

- see Pediatrics, P53

Table 40. Antibiotic Treatment of Pediatric Bacterial Infections

<table>
<thead>
<tr>
<th>Infection</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>MENINGITIS SEPSIS</td>
<td>GBS, E. coli, Listeria, Gram-negative bacilli</td>
<td>ampicillin + cefotaxime</td>
</tr>
<tr>
<td>Neurontal</td>
<td>Same pathogens as above and below</td>
<td>ampicillin + cefotaxime + vancomycin</td>
</tr>
<tr>
<td>1-3 mo</td>
<td>S. pneumoniae, H. influenzae type b (&gt;5 yr), meningococcus</td>
<td>ceftriazone + vancomycin</td>
</tr>
<tr>
<td>&gt;3 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>OTITIS MEDIA</td>
<td>S. pneumoniae, H. influenzae type b, M. catarrhalis</td>
<td>amoxicillin 80-90 mg/kg per day</td>
</tr>
<tr>
<td>1st line</td>
<td></td>
<td>clarithromycin 15 mg/kg/d bid (for penicillin allergy)</td>
</tr>
<tr>
<td>2nd line</td>
<td></td>
<td>90 mg/kg/d amoxicillin and 6.4 mg/kg/d clavulanate divided into bid dosage</td>
</tr>
<tr>
<td>Treatment failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>STREP PHARYNGITIS</td>
<td>Group A (β-hemolytic Streptococcus)</td>
<td>penicillin/amoxicillin or erythromycin (penicillin allergy)</td>
</tr>
<tr>
<td>URTI</td>
<td>E. coli, Proteus, H. influenzae, Pseudomonas, S. saprophyticus, Enterococcus, GBS</td>
<td>Oral: cephaalexin (older children) IV: ampicillin and aminoglycoside</td>
</tr>
<tr>
<td>PNEUMONIA</td>
<td>Viral, S. pneumoniae, C. trachomatis, B. pertussis, S. aureus, H. influenzae</td>
<td>cefuroxime ± macrolide (erythromycin) OR ampicillin ± macrolide</td>
</tr>
<tr>
<td>1-3 mo</td>
<td>Viral, S. pneumoniae, S. aureus, H. influenzae, Mycoplasma pneumoniae</td>
<td>ampicillin/amoxicillin or cefuroxime</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>As above</td>
<td>ampicillin/amoxicillin + macrolide or cefuroxime + macrolide</td>
</tr>
</tbody>
</table>

Red Flags for Abdominal Pain
- Significant weight loss or growth retardation (need growth chart)
- Fever
- Joint pain with objective physical findings
- Rash
- Rectal bleeding
- Rebound tenderness and radiation of pain to back, shoulders, or legs
- Pain wakes from sleep
- Severe diarrhea and encopresis
# Child Abuse and Neglect

- see Pediatrics, P14
- obligation to report any suspected/known case of child abuse or neglect to CAS yourself (do not delegate)
- document injuries
- consider skeletal survey x-rays (especially in non-ambulatory child), ophthalmology consult, CT head
- injury patterns associated with child abuse
  - HI: torn frenulum, dental injuries, bilateral black eyes, traumatic hair loss, diffuse severe CNS injury, retinal hemorrhage
  - Shaken Baby Syndrome: diffuse brain injury, subdural/SAH, retinal hemorrhage, minimal/no evidence of external trauma, associated bony fractures
  - skin injuries: bites, bruises/burns in shape of an object, glove/stocking distribution of burns, bruises of various ages, bruises in protected areas
  - bone injuries: rib fractures without major trauma, femur fractures age <1 yr, spiral fractures of long bones in non-ambulatory children, metaphyseal fractures in infants, multiple fractures of various ages, complex/multiple skull fractures
  - GU/GI injuries: chronic abdominal/perineal pain, injury to genitals/rectum, STI/pregnancy, recurrent vomiting or diarrhea

## Presentation of Neglect
- Failure to thrive, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents

## Procedures that may Require Sedation
- Setting fractures
- Reducing dislocations
- Draining abscesses
- Exploring wounds/ulcers/superficial infections
- Endoscopic examination
- Reduce patient anxiety/agitation for imaging/procedures

## Common Medications

### Table 41. Commonly Used Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>325-650 mg PO q4-6h prn</td>
<td>Pain control</td>
<td>Max 4 g daily</td>
</tr>
<tr>
<td>Activated charcoal</td>
<td>30-100 g PO in 250 mL H2O</td>
<td>Poisoning/overtase</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>325-650 mg PO q4h max 4g/d stroke/MI risk: 81-325 mg PO OD 160 mg chewed</td>
<td>Pain control</td>
<td>Cardiac prevention</td>
</tr>
<tr>
<td>β-blockers (metoprolol)</td>
<td>5 mg slow IV q5min x 3 if no contraindication</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>anxiety: 2-10 mg PO tid/qid alcohol withdrawal: 10-20 mg PO/IV q1h titrated to signs/symptoms</td>
<td>Anxiety Alcohol withdrawal</td>
<td></td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>1 mg/kg SC bid</td>
<td>Acute MI</td>
<td></td>
</tr>
<tr>
<td>Epinephrine</td>
<td>anaphylaxis: 0.1-0.5 mg IM; can repeat q10-15min</td>
<td>Anaphylaxis</td>
<td>Max 1 mg/dose</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>0.5-1.0 µg/kg IV</td>
<td>Procedural sedation</td>
<td>Very short acting narcotic (complication = apnea)</td>
</tr>
<tr>
<td>Flumazenil</td>
<td>0.3 mg IV bolus q5min x 3 doses</td>
<td>Reversal of procedural sedation</td>
<td>Benzodiazepine antagonist Can cause seizures/status epilepticus in chronic benzodiazepine users</td>
</tr>
<tr>
<td>Furosemide (Lasix®)</td>
<td>CHF: 40-80 mg IV HTN: 10-40 mg PO bid</td>
<td>Monitor for electrolyte imbalances</td>
<td></td>
</tr>
<tr>
<td>Glucose</td>
<td>0.5-1.0 g/kg (1-2 mL/kg) IV of D50W</td>
<td>Hypoglycemia/DKA</td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>2.5-5.0 mg PO/IM initial effective dose 6-20 mg/d</td>
<td>Psychosis</td>
<td>Monitor with Parkinson’s; results in CNS depression</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200-800 mg PO tid pm max 1,200 mg/d</td>
<td>Mild to moderate acute pain Analgesic and anti-inflammatory properties</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>bolus 5-10 U (0.2 U/kg) then 5-10 U (0.1 U/kg) per h</td>
<td>Hyperglycemia</td>
<td>Monitor blood glucose levels Consider K+ replacement, also measure blood glucose levels before administration</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>2-3 puffs inhaled tid-qid, max 12 puffs/d</td>
<td>Asthma</td>
<td>Contraindicated with peanut/soy allergy Caution with narrow-angie glaucoma</td>
</tr>
<tr>
<td>Lidocaine with epi</td>
<td>max 7 mg/kg SC</td>
<td>Local anesthetic</td>
<td>Not to be used in fingers, nose, toes, penis, ears</td>
</tr>
<tr>
<td>Lidocaine w/o epi</td>
<td>max 5 mg/kg SC</td>
<td>Local anesthetic</td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>anxiety: 0.5-2 mg PO/IM/IV q6-8h status epileptics: 4 mg IV repeat up to q5min</td>
<td>Anxiety Status epilepticus</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>50 µg/kg IV</td>
<td>Procedural sedation</td>
<td>Short acting benzodiazepine (complication = apnea when used with narcotic) Fentanyl and midazolam often used together for procedural sedation</td>
</tr>
</tbody>
</table>
### Table 41. Commonly Used Medications (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Morphine     | 15-30 mg PO q8-12h                                                  | Mild to moderate acute/chronic pain       | GI and constipation side effects
|              | 0.1-0.2 mg/kg max 15 mg IV q4h                                       | Prescribed in combination with NSAIDs     | DO NOT CRUSH, CUT, or CHEW                    |
|              |                                                                      | or acetaminophen                          |                                               |
| Naloxone     | 0.5-2 mg or 0.01-0.02 mg/kg initial bolus IV/IM/SL/SC or via ETT (2-2.5x IV dose), increase dose by 2 mg until response/max 10 mg | Comatose patient                          |                                               |
|              |                                                                      | Opioid overdose                           |                                               |
|              |                                                                      | Reversal in procedural sedation           |                                               |
| Nitroglycerin| acute angina: 0.3-0.6 mg SL q6min, OR 5 µg/min IV increasing by 5-20 µg/min q3-6min | Angina                                    | Not to be used with other antihypertensives |
|              |                                                                      | Acute MI                                  | Not in right ventricular MI                   |
| Percocet 10/325® | 1-2 tabs PO q6h pm                                                  | Moderate pain control                     | Oxycodone + acetaminophen                     |
|              |                                                                      |                                           | Max 4 g acetaminophen daily                   |
| Phenytoin    | Status epilepticus: see Table 17, ER25                              | Status epilepticus                        | Begin maintenance dose 12 h after loading dose |
|              |                                                                      |                                           | Continuous ECG, BP monitoring mandatory       |
| Polysporin®  | Apply to affected area bid-tid                                       | Superficial infections                    |                                               |
| Propofol     | 0.25-1 mg/kg IV                                                       | Procedural sedation                       | Short acting                                 |
|              |                                                                      |                                           | Anesthetic/sedative (complication = apnea, decreased BP) |
| Salbutamol   | 2 puffs inhaled q4-6h max 12 puffs/d                                 | Asthma                                    | Caution with cardiac abnormalities            |
| Thiamine     | 100 mg IV/IM initially, then 50-100 mg IM/IV/PO OD x 3d              | To treat/prevent Wernicke’s encephalopathy| Caution use in pregnancy                      |
| Tylenol #3®  | 1-2 tabs PO q4-6h pm                                                 | Pain control                              | Max 4 g acetaminophen daily                   |
References

Endocrinology

Tara Justice and Ilia Makedonov, chapter editors
Hart Stadnick and Kevin Yau, associate editors
Alex Cressman, EBM editor
Dr. Alice Cheng and Dr. Adam Millar, staff editors

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**Major Endocrine Organs**

**HYPOTHALAMUS**
- Corticotropin-RH (CRH)
- Gonadotropin-RH (GnRH)
- Thyrotropin-RH (TSH)
- Growth hormone-RH (GHRH)
- Antidiuretic hormone (ADH)*
- Oxytocin*

**THYROID GLAND**
- Triiodothyronine (T3)
- Thyroxine (T4)

**ADRENAL GLAND**
- Cortex
  - Aldosterone
  - Cortisol
  - Androgens
  - Medulla
  - Catecholamines

**TESTES**
- Testosterone

**PITUITARY GLAND**
- Anterior pituitary
  - Growth hormone (GH)
  - Thyroid-stimulating hormone (TSH)
  - Follicle-stimulating hormone (FSH)
  - Luteinizing hormone (LH)

- Posterior pituitary
  - Antidiuretic hormone (ADH)*
  - Oxytocin*

**PARATHYROID GLANDS**
- Parathyroid hormone (PTH)

**PANCREAS**
- Insulin
- Glucagon

**OVARIES**
- Estrogen
- Progesterone

*ADH and oxytocin are produced in the hypothalamus and stored in the posterior pituitary gland.

**Figure 1. Endocrine system**

**Dyslipidemias**

**Definition**
- Metabolic disorders characterized by elevations of fasting plasma LDL-cholesterol, and/or triglycerides (TG), and/or low HDL-cholesterol

**Overview of Lipid Transport**
- Lipoproteins are spherical complexes that consist of a lipid core surrounded by a shell of water-soluble cholesterol, apoproteins, and phospholipids
- Lipoproteins transport lipids within the body
- Apolipoproteins serve as enzyme co-factors, promote clearance of the particle by interacting with cellular receptors, and stabilize the lipoprotein micelle
Table 1. Lipoproteins

<table>
<thead>
<tr>
<th>Lipoprotein</th>
<th>Apolipoproteins</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chylomicron</td>
<td>B-48, C, E, A-I, A-II, A-IV</td>
<td>• Transports dietary TG from gut to adipose tissue and muscle</td>
</tr>
<tr>
<td><strong>Endogenous Pathway</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL</td>
<td>B-100, C, E</td>
<td>• Transports hepatic synthesized TG from liver to adipose tissue and muscle</td>
</tr>
<tr>
<td>IDL</td>
<td>B-100, E</td>
<td>• Product of hydrolysis of TG in VLDL by lipoprotein lipase resulting in depletion of TG core • Enriched in cholesterol esters</td>
</tr>
<tr>
<td>LDL</td>
<td>B-100</td>
<td>• Formed by further removal of residual TG from IDL core by hepatic lipase resulting in greater enriched particles with cholesterol esters • Transports cholesterol from liver to peripheral tissues (gonads, adrenals) • Acts as a reservoir for apolipoproteins</td>
</tr>
<tr>
<td>HDL</td>
<td>A-I, A-II, C, E</td>
<td>• Transports cholesterol from peripheral tissues to liver</td>
</tr>
</tbody>
</table>

Figure 2. Exogenous and endogenous biosynthetic lipid pathways

**Hypertriglyceridemia (Elevated Triglycerides)**

**PRIMARY HYPERTRIGLYCERIDEMIA**

Table 2. Primary Hypertriglyceridemias

<table>
<thead>
<tr>
<th>Hypertriglyceridemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Lipoprotein Lipase Deficiency</td>
<td>• Autosomal recessive deficiency of lipoprotein lipase or its cofactor</td>
<td>↑ TG • Chylomicrons Moderate ↑ in VLDL</td>
<td>• Hepatosplenomegaly • Splenic infarct • Anemia, granulocytopenia, thrombocytopenia 2° to hyperplasmia • Pancreatitis • Lipemia retinalis • Eruptive xanthomata</td>
<td>• Decrease dietary fat intake to &lt; 10% of total calories • Decrease dietary simple carbohydrates • Cook with medium chain fatty acids • Abstain from EtOH</td>
</tr>
<tr>
<td>Familial Hypertriglyceridemia</td>
<td>• Several genetic defects resulting in ↑ hepatic VLDL synthesis or ↓ removal of VLDL</td>
<td>↑ TG • VLDL</td>
<td>• Possible premature CAD • Develop syndrome of obesity, hypertriglyceridemia, hyperinsulinemia, and hyperuricemia in early adulthood</td>
<td>• Decrease dietary simple carbohydrates and fat intake • Abstain from EtOH • Fibrates or niacin</td>
</tr>
</tbody>
</table>
SECONDARY HYPERTRIGLYCERIDEMIA

Etiology
- endocrine: obesity/metabolic syndrome, hypothyroidism (more for high LDL, not TG), acromegaly, Cushing’s syndrome, DM
- renal: chronic renal failure, polyclonal and monoclonal hypergammaglobulinemia
- hepatic: chronic liver disease, hepatitis, glycogen storage disease
- drugs: alcohol, corticosteroids, estrogen, hydrochlorothiazide, retinoic acid, β-blockers without intrinsic sympathomimetic action (ISA), anti-retroviral drugs, atypical antipsychotics, oral contraceptive pills
- other: pregnancy

PRIMARY HYPERCHOLESTEROLEMIA

Table 3. Primary Hypercholesterolemias

<table>
<thead>
<tr>
<th>Hypercholesterolemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Hypercholesterolemia</td>
<td>1/500 in U.S. population • Autosomal codominant with high penetrance • More prevalent in French Canadian population • Defect in the normal LDL receptor on cell membranes</td>
<td>↑ LDL ↑ TC</td>
<td>Tendinous xanthomatosi (Achilles, patellar, and extensor tendons of hand) • Arcus cornealis • Xanthelasma • Heterozygotes: premature CAD, 50% risk of MI in men by age 30 • Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (&lt;20 yr) if untreated</td>
<td>• Heterozygotes: improvement of LDL with HMG-CoA reductase inhibitors, often in combination with ezetimibe or bile acid sequestrants • Homozygotes: partial control with portacaval shunt or LDL apheresis in conjunction with niacin; large dose atorvastatin is modestly effective</td>
</tr>
<tr>
<td>Polygenic Hypercholesterolemia</td>
<td>Most common • Few mild inherited defects in cholesterol metabolism</td>
<td>↑ TC ↑ LDL</td>
<td>Asymptomatic until vascular disease develops • No xanthomata • Homozygotes: manifest CAD and other vascular disease early in childhood and can be fatal (&lt;20 yr) if untreated</td>
<td>• HMG-CoA reductase inhibitors, ezetimibe, niacin, bile acid sequestrant</td>
</tr>
</tbody>
</table>

SECONDARY HYPERCHOLESTEROLEMIA

Etiology
- endocrine: hypothyroidism
- renal: nephrotic syndrome
- immunologic: monoclonal gammopathy
- hepatic: cholestatic liver disease (e.g. primary biliary cirrhosis)
- nutritional: diet, anorexia nervosa
- drugs: cyclosporin, anabolic steroids, carbamazepine

Combined Hyperlipidemia

Table 4. Primary Combined Hyperlipidemias

<table>
<thead>
<tr>
<th>Hyperlipidemia</th>
<th>Etiology/Pathophysiology</th>
<th>Labs</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familial Combined Hyperlipidemia</td>
<td>Over-population of VLDL and associated ↑ LDL 2x to excess hepatic synthesis of apolipoprotein B • Autosomal dominant</td>
<td>↑ TC + TG ↑ VLDL ↑ LDL</td>
<td>Xanthelasma • CAD and other vascular disease • Xanthomata • Tuberous, eruptive, palmar xanthomata • Impaired glucose tolerance • CAD and PAD</td>
<td>• Weight reduction • Decrease fat, cholesterol, and EtOH in diet • HMG-CoA reductase inhibitors (statins) • Niacin, fibrates, ezetimibe</td>
</tr>
<tr>
<td>Dysbetalipoproteinemia</td>
<td>Abnormal apolipoprotein E</td>
<td>↑ TC + TG ↑ VLDL ↑ LDL</td>
<td>Tuberous, eruptive, palmar xanthomata • Impaired glucose tolerance • CAD and PAD • Tubular, eruptive</td>
<td>• Weight reduction • Decrease simple carbohydrates, fat, cholesterol, and EtOH in diet • HMG-CoA reductase inhibitors (statins) • Niacin, fibrates, ezetimibe</td>
</tr>
</tbody>
</table>
Dyslipidemia and the Risk for Coronary Artery Disease

- increased LDL is a major risk factor for atherosclerosis and CAD as LDL is the major atherogenic lipid particle
- increased HDL is associated with decreased cardiovascular disease and mortality
- moderate hypertriglyceridemia (triglyceride level 2.3–9 mmol/L) is an independent risk factor for CAD, especially in people with DM and in post-menopausal women
- treatment of hypertriglyceridemia has not been shown to reduce CAD risk

Screening
- screen men over age 40, women over age 50 or post-menopausal
- if following risk factors present, screen at any age
  - DM
  - current cigarette smoking or COPD
  - HTN (sBP >140, dBP >90)
  - obesity (BMI >27 kg/m²)
  - family history of premature CAD
  - clinical signs of hyperlipidemia (xanthelasma, xanthoma, arcus cornealis)
  - evidence of atherosclerosis
  - inflammatory disease (rheumatoid arthritis, SLE, psoriatic arthritis, ankylosing spondylitis, inflammatory bowel disease)
  - HIV infection on highly active anti-retroviral therapy (HAART)
  - chronic kidney disease (estimated GFR <60 mL/min/1.73 m²)
  - erectile dysfunction
  - screen children with a family history of hypercholesterolemia or chylomicronemia

Factors Affecting Risk Assessment
- metabolic syndrome
- apolipoprotein B (apo B)
  - each atherogenic particle (VLDL, IDL, LDL, and lipoprotein A) contains one molecule of apo B
  - serum [apo B] reflects the total number of particles and may be useful in assessing cardiovascular risk and adequacy of treatment in high risk patients and those with metabolic syndrome
- C-reactive protein (hs-CRP) levels
  - highly sensitive acute phase reactant
  - may be clinically useful in identifying those at a higher risk of cardiovascular disease than predicted by the global risk assessment

Treatment of Dyslipidemias

Approach to Treatment
For clinical guidelines see Can J Cardiol 2012;28:151-167
- estimate 10 yr risk of CAD using Framingham model
- establish treatment targets according to level of risk

Table 5. Target Lipids by Risk Group

<table>
<thead>
<tr>
<th>Level of Risk</th>
<th>Definition (10 Yr Risk of CAD)</th>
<th>Initiate Treatment if:</th>
<th>Primary Target LDL-C</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Risk ≥20%, or Clinical atherosclerosis, Abdominal aortic aneurysm, DM &gt;15 yr duration and age older than 30 yr, DM with age older than 40 yr, Microvascular disease, High risk kidney disease, High risk HTN</td>
<td>Consider treatment in all patients</td>
<td>≤2 mmol/L or ≥50% ↓ in LDL</td>
<td>apo B ≤0.80 g/L or non-HDL-C ≤2.6 mmol/L</td>
</tr>
<tr>
<td>Moderate</td>
<td>Risk 10-19%</td>
<td>LDL &gt;3.5 mmol/L, apo B &gt;1.2 g/L or non-HDL-C &gt;4.3 mmol/L</td>
<td>≤2 mmol/L or ≥50% ↓ in LDL</td>
<td>apo B &lt;0.80 g/L or non-HDL-C &lt;2.6 mmol/L</td>
</tr>
<tr>
<td>Low</td>
<td>Risk &lt;10%</td>
<td>LDL ≤5.0 mmol/L, Familial hypercholesterolemia</td>
<td>≥50% ↓ in LDL</td>
<td></td>
</tr>
</tbody>
</table>
### Disorders of Glucose Metabolism

**Overview of Glucose Regulation**

- **Beta cells** of the pancreas stimulated to release insulin into the blood stream.
- Increased in blood glucose levels.
- Liver breaks down glycogen stores and releases glucose into the blood.
- **Insulin**
  - Body cells take up more glucose.
  - Liver takes up excess glucose and stores it as glycogen.
- **Glucagon**
  - Alpha cells of the pancreas stimulated to release glucagon into the blood.
  - Decrease in blood glucose levels.

**Pre-Diabetes (Impaired Glucose Tolerance/Impaired Fasting Glucose)**

- 1-5% per yr go on to develop DM.
- 50-80% revert to normal glucose tolerance.
- Weight loss may improve glucose tolerance.
- Increased risk of developing macrovascular complications (IGT > IFG).
- Lifestyle modifications decrease progression to DM by 58%.

**Diagnostic Criteria (CDA Guidelines)**

- Impaired fasting glucose (IFG): fasting blood glucose (FBG) 6.1-6.9 mmol/L.
- Impaired glucose tolerance (IGT): 2h 75 g oral glucose tolerance test (OGTT) 7.8-11.0 mmol/L.
- HbA1c: 6.0-6.4%.

---

**Table 6. Treatment of Hypercholesterolemia and Hypertriglyceridemia**

<table>
<thead>
<tr>
<th>Treatment of Hypercholesterolemia</th>
<th>Treatment of Hypertriglyceridemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative: 4-6 mo trial unless high risk group, in which case medical treatment should start immediately</strong></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
</tr>
<tr>
<td>- Decrease fat: &lt;30% calories</td>
<td></td>
</tr>
<tr>
<td>- Decrease saturated fat: &lt;10% calories</td>
<td></td>
</tr>
<tr>
<td>- Decrease cholesterol: &lt;200 mg/d</td>
<td></td>
</tr>
<tr>
<td>- Increase fibre: &gt;30 g/d</td>
<td></td>
</tr>
<tr>
<td>- Smoking cessation</td>
<td></td>
</tr>
<tr>
<td>- Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</td>
<td></td>
</tr>
<tr>
<td>- Weight loss: target BMI &lt;25</td>
<td></td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
</tr>
<tr>
<td>- HMG-CoA reductase inhibitors, ezetimibe, bile acid sequestrants, niacin (see Common Medications, E53)</td>
<td></td>
</tr>
<tr>
<td><strong>Conservative: 4-6 mo trial</strong></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td></td>
</tr>
<tr>
<td>- Decrease fat and simple carbohydrates</td>
<td></td>
</tr>
<tr>
<td>- Increase omega-3 polyunsaturated fatty acid</td>
<td></td>
</tr>
<tr>
<td>- Control blood sugars</td>
<td></td>
</tr>
<tr>
<td>- Decrease alcohol intake to ≤1-2 drinks/d</td>
<td></td>
</tr>
<tr>
<td>- Smoking cessation</td>
<td></td>
</tr>
<tr>
<td>- Aerobic exercise: ≥150 min/wk in bouts of ≥10 min</td>
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</tr>
<tr>
<td>- Weight loss: target BMI &lt;25</td>
<td></td>
</tr>
<tr>
<td><strong>Medical</strong></td>
<td></td>
</tr>
<tr>
<td>- Fibrates, niacin (see Common Medications, E53)</td>
<td></td>
</tr>
</tbody>
</table>

**Indications:**
- Failed conservative measures
- TG >10 mmol/L (885 mg/dL) to prevent pancreatitis
- Combined hyperlipidemia
Diabetes Mellitus

Definition
- syndrome of disordered metabolism and inappropriate hyperglycemia secondary to an absolute/relative deficiency of insulin, or a reduction in biological effectiveness of insulin, or both

Diagnostic Criteria (CDA Guidelines)
- any one of the following is diagnostic
  - FPG ≥7.0 mmol/L (fasting = no caloric intake for at least 8 h) OR
  - 2h 75 g OGTT ≥11.1 mmol/L OR
  - random PG ≥11.1 mmol/L OR
  - HbA1c ≥6.5% (not for diagnosis of suspected Type 1 DM, children, adolescents, or pregnant women)
- in the presence of hyperglycemia symptoms (polyuria, polydipsia, polyphagia, weight loss, blurry vision), a confirmatory test is not required
- in the absence of hyperglycemic symptoms, a repeat confirmatory test is required to make the diagnosis of diabetes

Etiology and Pathophysiology

Table 7. Etiologic Classification of Diabetes Mellitus

| I. Type 1 DM (immune-mediated β cell destruction, usually leading to absolute insulin deficiency) |
| II. Type 2 DM (ranges from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance 2nd to β cell dysfunction) |
| III. Other Specific Causes of DM a. Genetic defects of β cell function (e.g. MODY – Maturity-Onset Diabetes of the Young) or insulin action b. Diseases of the exocrine pancreas:  • Pancreatitis, pancreatectomy, neoplasia, cystic fibrosis, hemochromatosis (“bronze diabetes”) c. Endocrinopathies:  • Acromegaly, Cushing’s syndrome, glucagonoma, pheochromocytoma, hyperthyroidism d. Drug-induced:  • Glucocorticoids, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, clozapine e. Infections:  • Congenital rubella, CMV, coxsackie f. Genetic syndromes associated with DM:  • Down’s syndrome, Klinefelter’s syndrome, Turner’s syndrome |
| IV. Gestational Diabetes Mellitus (see Obstetrics, OB27) |

Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Onset</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Usual</td>
<td>&lt;30 yr of age</td>
<td>&gt;40 yr of age</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>More common in Caucasians</td>
<td>More common in Blacks, Hispanics, Aboriginals, and Asians</td>
</tr>
<tr>
<td>Etiology</td>
<td>Autoimmune</td>
<td>Complex and multifactorial</td>
</tr>
<tr>
<td>Genetics</td>
<td>Monozigotic twin concordance is 30-40%</td>
<td>Greater heritability than type 1 DM</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Synergistic effects of genetic, immune, and environmental factors that cause β cell destruction resulting in impaired insulin secretion</td>
<td>Impaired insulin secretion, peripheral insulin resistance (likely due to receptor and post receptor abnormalities), and excess hepatic glucose production</td>
</tr>
</tbody>
</table>

Blood Glucose Control in Type 2 DM – UKPDS 33
Lancet 1998;352:837-853
Study: RCT (mean follow-up 10 yr).
Patients: 3,867 patients with newly diagnosed type 2 DM (mean age 53 yr, 61% men, 81% white, mean fasting plasma glucose [FPG] 8.1-15.0 mmol/L).
Exclusions included severe cardiovascular disease, renal disease, retinopathy, and others.
Intervention: Intensive treatment with a sulfonylurea or insulin (target FPG <6 mmol/L) vs. conventional treatment with diet alone (target FPG <16 mmol/L without hyperglycemic symptoms).
Main Outcomes: DM-related endpoints (MI, angina, heart failure, stroke, renal failure, amputation, retinopathy, blindness, death from hyperglycemia or hypoglycemia), DM-related death, and all-cause mortality.
Results: Patients allocated to intensive treatment had lower median HbA1c levels (p<0.001).

Outcome | RRR % (p value)
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>DM-related endpoint</td>
<td>12 (0.029)</td>
</tr>
<tr>
<td>DM-related death</td>
<td>10 (0.34)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6 (0.44)</td>
</tr>
</tbody>
</table>

Patients allocated to intensive therapy had more hypoglycemic episodes and greater weight gain.
Conclusion: Intensive blood glucose control reduces microvascular but not macrovascular complications in type 2 DM.
Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Natural History</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>≤7.0% in 58% of patients</td>
<td>≤8.0% in 60% of patients</td>
</tr>
<tr>
<td>Circulating Autoantibodies</td>
<td>Islet cell Ab present in up to 60-85%</td>
<td>&lt; 10%</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Personal history of other autoimmune diseases, including Graves’, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia</td>
<td>Age &gt; 40 yr</td>
</tr>
<tr>
<td>Body Habitus</td>
<td>Normal to thin</td>
<td>Typically overweight with increased central obesity</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Lifestyle modification</td>
</tr>
<tr>
<td>Acute Complication</td>
<td>Diabetic ketoacidosis (DKA) in severe cases</td>
<td>Hyperosmolar hyperglycemic state (HHS)</td>
</tr>
<tr>
<td>Screening</td>
<td>Subclinical proclivity can be detected in first and second-degree relatives of those with type 1 DM</td>
<td>Screen individuals with risk factors</td>
</tr>
</tbody>
</table>

**Conclusions**
- Targeting intensive glycemic control versus targeting conventional glycemic control for type 2 DM.
- Study: Systematic review of randomized clinical trials of intensive glycemic control in adults with type 2 DM.
- Patients: Twenty-two trials randomized 16,166 patients with type 2 DM to intensive control and 13,880 patients with type 2 DM to conventional glycemic control.
- Interventions: Intensive glycemic control (HbA1c <6.5%) versus conventional glycemic control (determined by local guidelines).
- Primary Outcome: All-cause mortality, cardiovascular mortality, and mishap.
- Results: There was no significant difference between targeting intensive and conventional glycemic control.
- Conclusions: Intensive glycemic control may not reduce all-cause mortality and cardiovascular mortality compared to conventional glycemic control. Intensive glycemic control reduced the risk of microvascular complications, while increasing the risk of hypoglycemia. Intensive glycemic control may also reduce the risk of non-fatal MI in trials exclusively dealing with glycemic control in usual care settings.

**Canadian Diabetes Guidelines 2013**

<table>
<thead>
<tr>
<th>Target</th>
<th>Hba1c</th>
<th>Fasting plasma glucose (72-126 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤7.0%</td>
<td>4-7 mmol/L</td>
</tr>
<tr>
<td>2h post-prandial glucose (90-180 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-10 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>As per high risk group if age &gt; 60 or age &gt; 50 if DM duration &gt; 15 yr</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 DM: The Look AHEAD Trial**

- Study: ICT, with 9.6 yr of median follow-up.
- Population: 5,145 overweight or obese patients with type 2 DM.
- Intervention: Intensive lifestyle intervention promoting weight loss through decreased caloric intake and increased physical activity (intervention) or DM support and education (control).
- Primary Outcome: First occurrence of death from cardiovascular (CV) cause, non-fatal MI, non-fatal stroke, or hospitalization for angina.
- Results: Although the intensive lifestyle intervention produced greater weight loss and reductions in glycated hemoglobin, the intervention did not significantly reduce the risk of CV morbidity or mortality.
- Conclusions: An intensive lifestyle intervention focusing on weight loss did not significantly reduce the rate of cardiovascular events in overweight or obese adults with type 2 DM.

**Treatment of Diabetes**

- **Glycemic Targets**
  - HbA1c reflects glycemic control over 3 mo and is a measure of patient’s long-term glycemic control.
  - In most individuals with type 1 or type 2 DM (especially younger patients) should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications.
  - More intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of DM with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia.
  - Less stringent HbA1c targets (7.1-8.5%) may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to attain HbA1c <7.0% despite intensified basal and bolus insulin therapy.
  - There may be harm associated with strategy to target HbA1c <6.0% (see ACCORD trial, E9).

- **Diet**
  - Daily carbohydrate intake 45-60% of energy, protein 15-20% of energy, and fat <35% of energy.
  - Intake of saturated fats <7% and polyunsaturated fats <10% of total calories each.
  - Limit sodium, alcohol, and caffeine intake.
  - Type 1: Carbohydrate counting is used to titrate insulin regimen.
  - Type 2: Weight reduction.

- **Natural History**
  - After initial presentation, honeymoon period often occurs where glycemic control can be achieved with little or no insulin treatment as residual cells are still able to produce insulin.
  - Once these cells are destroyed, there is complete insulin deficiency.
  - Early on, glucose tolerance remains normal despite insulin resistance as β cells compensate with increased insulin production.
  - As insulin resistance and compensatory hyperinsulinism continue, the β cells are unable to maintain the hyperinsulinemic state which results in glucose intolerance and DM.

- **Risk Factors**
  - Personal history of other autoimmune diseases, including Graves’, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia.
  - Family history of autoimmune diseases.
  - Age > 40 yr.
  - Abdominal obesity/overweight.
  - First-degree relative with DM.
  - Race/ethnicity (Black, Aboriginal, Hispanic, Asian-American, Pacific Islander).
  - Hx of IGT or IIS.
  - HTN.
  - Dyslipidemia.
  - Medications e.g. 2nd generation antipsychotics.
  - PCOS.
  - Hx of gestational DM or macrosomic baby (>9 lb or 4 kg).

- **Screening**
  - Subclinical prodrome can be detected in first and second-degree relatives of those with type 1 DM by the presence of pancreatic islet autoantibodies.

**Table 8. Comparison of Type 1 and Type 2 Diabetes Mellitus (continued)**

<table>
<thead>
<tr>
<th>Natural History</th>
<th>Type 1</th>
<th>Type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>≤7.0% in 58% of patients</td>
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<td>&lt; 10%</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Personal history of other autoimmune diseases, including Graves’, myasthenia gravis, autoimmune thyroid disease, celiac disease, and pernicious anemia</td>
<td>Age &gt; 40 yr</td>
</tr>
<tr>
<td>Body Habitus</td>
<td>Normal to thin</td>
<td>Typically overweight with increased central obesity</td>
</tr>
<tr>
<td>Treatment</td>
<td>Insulin</td>
<td>Lifestyle modification</td>
</tr>
<tr>
<td>Acute Complication</td>
<td>Diabetic ketoacidosis (DKA) in severe cases</td>
<td>Hyperosmolar hyperglycemic state (HHS)</td>
</tr>
<tr>
<td>Screening</td>
<td>Subclinical proclivity can be detected in first and second-degree relatives of those with type 1 DM</td>
<td>Screen individuals with risk factors</td>
</tr>
</tbody>
</table>

**Conclusions**
- Targeting intensive glycemic control versus targeting conventional glycemic control for type 2 DM.
- Study: Systematic review of randomized clinical trials of intensive glycemic control in adults with type 2 DM.
- Patients: Twenty-two trials randomized 16,166 patients with type 2 DM to intensive control and 13,880 patients with type 2 DM to conventional glycemic control.
- Interventions: Intensive glycemic control (HbA1c <6.5%) versus conventional glycemic control (determined by local guidelines).
- Primary Outcome: All-cause mortality, cardiovascular mortality, and mishap.
- Results: There was no significant difference between targeting intensive and conventional glycemic control.
- Conclusions: Intensive glycemic control may not reduce all-cause mortality and cardiovascular mortality compared to conventional glycemic control. Intensive glycemic control reduced the risk of microvascular complications, while increasing the risk of hypoglycemia. Intensive glycemic control may also reduce the risk of non-fatal MI in trials exclusively dealing with glycemic control in usual care settings.

**Canadian Diabetes Guidelines 2013**

<table>
<thead>
<tr>
<th>Target</th>
<th>HbA1c</th>
<th>Fasting plasma glucose (72-126 mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤7.0%</td>
<td>4-7 mmol/L</td>
</tr>
<tr>
<td>2h post-prandial glucose (90-180 mg/dL)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5-10 mmol/L</td>
<td></td>
</tr>
<tr>
<td>Lipids</td>
<td>As per high risk group if age &gt; 60 or age &gt; 50 if DM duration &gt; 15 yr</td>
<td></td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80</td>
<td></td>
</tr>
</tbody>
</table>

**Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 DM: The Look AHEAD Trial**

- Study: ICT, with 9.6 yr of median follow-up.
- Population: 5,145 overweight or obese patients with type 2 DM.
- Intervention: Intensive lifestyle intervention promoting weight loss through decreased caloric intake and increased physical activity (intervention) or DM support and education (control).
- Primary Outcome: First occurrence of death from cardiovascular (CV) cause, non-fatal MI, non-fatal stroke, or hospitalization for angina.
- Results: Although the intensive lifestyle intervention produced greater weight loss and reductions in glycated hemoglobin, the intervention did not significantly reduce the risk of CV morbidity or mortality.
- Conclusions: An intensive lifestyle intervention focusing on weight loss did not significantly reduce the rate of cardiovascular events in overweight or obese adults with type 2 DM.

**Treatment of Diabetes**

- **Glycemic Targets**
  - HbA1c reflects glycemic control over 3 mo and is a measure of patient’s long-term glycemic control.
  - Therapy in most individuals with type 1 or type 2 DM (especially younger patients) should be targeted to achieve a HbA1c ≤7.0% in order to reduce the risk of microvascular and if implemented early in the course of disease, macrovascular complications.
  - More intensive glucose control, HbA1c <6.5%, may be targeted in patients with a shorter duration of DM with no evidence of significant CVD and longer life expectancy, to further reduce risk of nephropathy and retinopathy, provided this does not result in a significant increase in hypoglycemia.
  - Less stringent HbA1c targets (7.1-8.5%) may be more appropriate in type 1 and type 2 patients with limited life expectancy, higher level of functional dependency, a history of recurrent severe hypoglycemia, multiple comorbidities, extensive CAD, or a failure to attain HbA1c <7.0% despite intensified basal and bolus insulin therapy.
  - There may be harm associated with strategy to target HbA1c <6.0% (see ACCORD trial, E9).

- **Diet**
  - Daily carbohydrate intake 45-60% of energy, protein 15-20% of energy, and fat <35% of energy.
  - Intake of saturated fats <7% and polyunsaturated fats <10% of total calories each.
  - Limit sodium, alcohol, and caffeine intake.
  - Type 1: Carbohydrate counting is used to titrate insulin regimen.
  - Type 2: Weight reduction.
**Medical Treatment: Oral Antihyperglycemic Agents and/or Incretin Therapy (Type 2 DM)**
- initiate oral antihyperglycemic therapy and/or incretin therapy within 2-3 mo if lifestyle management does not result in glycemic control
- if HbA1c >8.5%, initiate pharmacologic therapy immediately and consider combination oral therapy or insulin immediately
- continue to add additional pharmacologic therapy in a timely fashion to achieve target HbA1C within 3-6 months of diagnosis
- see Common Medications, E52 for details on antihyperglycemic agents

**Medical Treatment: Insulin (Figure 5)**
- used for type 1 DM at onset, may be used in type 2 DM at any point in treatment
- routes of administration: subcutaneous injections, continuous subcutaneous insulin infusion pump, IV infusion (regular insulin only)
- bolus insulins: short-acting (Insulin regular), rapid-acting analogue (Insulin aspart, Insulin lispro, Insulin glulisine)
- basal insulins: intermediate-acting (Insulin NPH), long-acting analogue (Insulin detemir, Insulin glargine)
- premixed insulins (combination of basal and bolus insulins) available but not used regularly
- estimated total daily insulin requirement: 0.5-0.7 units/kg (often start with 0.3-0.5 units/kg/d)

**Table 9. Available Insulin Formulations**

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRANDIAL (BOLUS) INSULINS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid-acting insulin analogues</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Insulin aspart (NovoRapid®)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td>- Insulin lispro (Humalog®)</td>
<td>10-15 min</td>
<td>1-2 h</td>
<td>3.5-4.75 h</td>
</tr>
<tr>
<td>- Insulin glulisine (Apidra®)</td>
<td>10-15 min</td>
<td>1-1.5 h</td>
<td>3-5 h</td>
</tr>
<tr>
<td>Short-acting insulins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Humulin R®</td>
<td>30 min</td>
<td>2-3 h</td>
<td>6.5 h</td>
</tr>
<tr>
<td>- Novolin Toronto®</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effects of Intensive Glucose Lowering in Type 2 DM: The ACCORD Trial**
*NEJM 2010;362:1563-1574*

**Study:** Multicentre RCT  
**Patients:** 10,251 patients (mean age 62.2) with type 2 DM, and cardiovascular risk factors.  
**Intervention:** Intensive therapy targeting a HbA1c level of less than 6.0% or standard therapy targeting 7.0-7.9%.  
**Outcomes:** First occurrence of nonfatal MI, nonfatal stroke, or death from CV causes.  
**Results:** The intensive therapy arm was stopped early (3.5 yr vs. 5.6 yr planned) due to evidence of increased mortality. There was no difference in primary outcome for either study arm. There was a significant increase in all-cause mortality, CV mortality, nonfatal MI, and CHF in the intensive therapy group. There were increased rates of all hyperglycemic events, any nonhyperglycemic serious adverse events, fluid retention, and weight gain >10 kg, but lower systolic and diastolic blood pressure in the intensive therapy group. There was an increased incidence of elevated ALT (>3 times upper limit) and ACE drug use in the standard therapy group.  
**Conclusions:** Intensive glucose lowering therapy in type 2 DM does not improve clinic outcomes and actually increases the risk of mortality with more adverse events compared to standard therapy. Additional research is required to discern the cause.

**Effects of Intensive Blood Pressure Control in Type 2 DM: The ACCORD Trial**
*NEJM 2010;362:1575-1585*

**Study:** RCT, unblinded with 4.7 yr of mean follow-up  
**Population:** 4,733 patients with type 2 DM, risk factors for cardiovascular (CV) disease, systolic blood pressure (sBP) between 130-180 mmHg.  
**Intervention:** sBP control less than 120 mmHg (intensive) or 140 mmHg (standard).  
**Primary Outcomes:** Major CV event (composite nonfatal MI, nonfatal stroke, or CV-related death).  
**Results:** Mean number of medications at 1 yr for intensive therapy was 3.4 (95% CI 3.4-3.5) versus 2.1 (95% CI 2.1-2.2) for standard therapy. There was a significant increase in all serious adverse events in the intensive treatment arm (3.2% vs. 1.2%, p<0.001); especially bradycardia or arrhythmia (0.9% vs. 0.13%, p=0.02) and hyperkalemia (0.4% vs. 0.04%, p=0.01). There was no significant difference in primary outcomes in the two study arms, or all-cause mortality. There was a significant reduction in any stroke (0.32%/yr vs. 0.53%/yr, p=0.01) and nonfatal stroke incidences (0.30%/yr vs. 0.47%/yr, p=0.03) in the intensive therapy arm.  
**Conclusions:** Intensive BP lowering to less than 120 mmHg vs. 140 mmHg in patients with type 2 DM and CV risk factors does not reduce major CV event risk reduction except for stroke events.

**Effects of Combination Lipid Therapy in Type 2 DM: The ACCORD Trial**
*NEJM 2010;362:1583-1594*

**Study:** RCT, double blinded trial with 4.7 yr of mean follow-up  
**Population:** 5,518 patients with type 2 DM.  
**Intervention:** Statin with or without fibrate therapy.  
**Primary Outcome:** Major cardiovascular (CV) event (composite nonfatal MI, nonfatal stroke, or CV-related death).  
**Results:** No significant differences in primary outcome between the two arms. No difference in all MI, all stroke, or all-cause mortality between study arms.  
**Conclusions:** The addition of fibrate therapy to statin therapy in patients with type 2 DM does not reduce major CV event risk.
Table 9. Available Insulin Formulations (continued)

<table>
<thead>
<tr>
<th>Insulin Regimen</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASEL INSULINS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Humulin N®</td>
<td>1-3 h</td>
<td>5-8 h</td>
<td>Up to 18 h</td>
</tr>
<tr>
<td>• Novolin NPH®</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting basal insulin analogues</td>
<td>90 min</td>
<td>Not applicable</td>
<td>Up to 24 h (glargine 24 h, detemir 16-24 h)</td>
</tr>
<tr>
<td>Insulin detemir (Levemir®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin glargine (Lantus®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**PRE-MIXED INSULINS**

- Premixed regular insulin – NPH: 1:1 ratio of rapid and intermediate insulin
- Premixed insulin analogues: \(25/75\%\) ratio of rapid and intermediate insulin
- Biphasic insulin aspart (NovoMix 30®)
- Insulin lispro/lispro protamine (Humalog Mix25® and Mix50®)

**Figure 5. Duration of activity of different insulins**

**Insulin Regimens**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2 DM</td>
<td>Oral hypoglycemic agent + basal insulin</td>
</tr>
<tr>
<td>Type 1 DM</td>
<td>Multiple daily injections (MDI)</td>
</tr>
<tr>
<td>Split-mixed</td>
<td>Estimated total insulin requirement is 0.5-0.7 U/kg</td>
</tr>
</tbody>
</table>

- Basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia
- Antihyperglycemic agents (e.g. sitagliptin, saxagliptin, linagliptin) that inhibit DPP-IV, which is an enzyme that degrades endogenous incretin hormones like GLP-1
- Incretin hormones stimulate glucose-dependent insulin secretion and inhibit glucagon release from the pancreas
- DPP-IV Inhibitors
- GLP-1 Analogues (Incretins)
- Human glucagon-like peptide-1 analogues: exenatide, liraglutide
- These activate GLP-1 causing increased insulin secretion, decreased inappropriate glucagon secretion, increased B-cell growth/replication, slowed gastric emptying, and decreased food intake
- Associated with weight loss
- Subcutaneous formulation

**Table 10. Insulin Regimens for Type 2 DM and Type 1 DM**

<table>
<thead>
<tr>
<th>Insulin Type (trade name)</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biphasic insulin aspart (NovoMix 30®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin lispro/lispro protamine (Humalog Mix25® and Mix50®)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 11. Titrating Insulin Doses**

<table>
<thead>
<tr>
<th>Hyperglycemic Reading</th>
<th>Insulin Correction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High AM sugar</td>
<td>Increase bedtime basal insulin</td>
</tr>
<tr>
<td>High lunch sugar</td>
<td>Increase AM rapid/regular insulin</td>
</tr>
<tr>
<td>High supper sugar</td>
<td>Increase lunch rapid/regular insulin, or increase AM basal insulin</td>
</tr>
<tr>
<td>High bedtime sugar</td>
<td>Increase supper rapid/regular insulin</td>
</tr>
</tbody>
</table>

**Variable Insulin Dose Schedule (“Sliding/Supplemental/Correction Scale”)**

- For patients on Basal-Bolus MDI regimen: patient takes usual doses of basal insulin but varies doses of bolus insulin based on BG reading at time of dose
- Use baseline bolus insulin dose when within BG target range; add or subtract units when above or below target
- When used in hospital (including perioperative management of DM) patient should also receive basal insulin to prevent fluctuations in blood sugar levels or long periods of hyperglycemia

**Figure 6. Duration of activity of different insulins**

**Effect of Mediterranean Diet in Preventing Cardiovascular Events in Type 2 DM: The PREDIMED Trial**

*NEJM* 2013;368:1279-1300

**Methods:** Investigators randomized 7,447 patients with type 2 DM or other high cardiovascular risk factors to Mediterranean diet supplemented with extra-virgin olive oil, Mediterranean diet supplemented with mixed nuts, or control diet with advice to reduce dietary fat.

**Primary Outcome:** Major cardiovascular (CV) event (MI, stroke, or death from CV causes).

**Results:** Both Mediterranean diets were associated with a reduced incidence of major CV events compared to the control diet.

**Conclusion:** A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, stroke, and CV death in those at high risk for CV disease.

**Conversion Chart for Percentage HbA1c**

<table>
<thead>
<tr>
<th>Average blood sugar level (mmol/L)</th>
<th>Hemoglobin A1c (% HbA1c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>17</td>
<td>12%</td>
</tr>
<tr>
<td>16</td>
<td>11%</td>
</tr>
<tr>
<td>15</td>
<td>10%</td>
</tr>
<tr>
<td>14</td>
<td>9%</td>
</tr>
<tr>
<td>13</td>
<td>8%</td>
</tr>
<tr>
<td>12</td>
<td>7%</td>
</tr>
<tr>
<td>11</td>
<td>6%</td>
</tr>
</tbody>
</table>

**The 8 Is Precipitating DKA**

- Infection
- Ischemia or Infarction
- Iatrogenic (glucocorticoids)
- Intoxication
- Insulin overdose
- Initial presentation
- Intra-abdominal process (e.g. pancreatitis, cholecystitis)
- Intraoperative/perioperative stress
• construction of a supplemental sliding scale for a patient on anti-hyperglycemics
  ▪ Correction Factor (CF) = 100/Total Daily Dose of insulin (TDD)
  ▪ BG <4: call MD and give 15 g carbohydrates
  ▪ BG between 4 to 8: no additional insulin
  ▪ BG between 8 to (8 + CF): give one additional unit
  ▪ BG between (8 + CF) to (8 + 2CF): give two additional units
  ▪ BG between (8 + 2CF) to (8 + 3CF): give three additional units

**Insulin Pump Therapy: Continuous Subcutaneous Insulin Infusion (CSII)**
• external battery-operated device provides continuous basal dose of rapid-acting insulin analogue (aspart, glulisine, or lispro) through small subcutaneous catheter
• at meals, patient programs pump to deliver insulin bolus
• provides improved quality of life and flexibility
• risk of DKA if pump is inadvertently disconnected
• coverage available for insulin pumps for individuals with Type 1 DM varies by province

### Acute Complications

**Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States**

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Diabetic Ketoacidosis (DKA)</th>
<th>Hyperosmolar Hyperglycemic State (HHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyuria, polydipsia, polyphagia with marked fatigue, N/V</td>
<td></td>
<td>Onset is insidious ( \rightarrow ) preceded by weakness, polyuria, polydipsia</td>
</tr>
<tr>
<td>Dehydration (orthostatic changes)</td>
<td></td>
<td>History of decreased fluid intake</td>
</tr>
<tr>
<td>LOC may be ( \downarrow ) with ketoacidosis or with high serum osmolality (osm &gt;330 mmol/L)</td>
<td></td>
<td>History of ingesting large amounts of glucose containing fluids</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td></td>
<td>Dehydration (orthostatic changes)</td>
</tr>
<tr>
<td>Fruity smelling breath</td>
<td></td>
<td>↓ LOC ( \rightarrow ) lethargy, confusion, comatose due to high serum osmolality</td>
</tr>
<tr>
<td>Kussmaul’s respiration</td>
<td></td>
<td>Kussmaul’s respiration is absent unless the underlying precipitant has also caused a metabolic acidosis</td>
</tr>
</tbody>
</table>

| Serum | | |
| \( \uparrow \) BG (typically 11-55 mmol/L, \( \downarrow \) Na\(^+\) (2\(^{nd}\) to hyperglycemia \( \rightarrow \) for every \( \uparrow \) in BG by 10 mmol/L) there is a \( \downarrow \) in Na\(^+\) by 3 mmol/L) | \( \uparrow \) TG (typically 44.4-133.2 mmol/L) |
| Normal or \( \uparrow \) K\(^+\), \( \downarrow \) HCO\(_3\)\(^-\), \( \uparrow \) BUN, \( \uparrow \) Cr, ketonemia, \( \downarrow \) PO\(_4\)\(^{3-}\), \( \uparrow \) osmolality | In mild dehydration, may have hyponatremia (spurious 2\(^{nd}\) to hyperglycemia \( \rightarrow \) for every \( \uparrow \) in BG by 10 mmol/L there is a \( \downarrow \) in Na\(^+\) by 3 mmol/L) |
| \( \uparrow \) osmolality | \( \uparrow \) osmolality |

| ABG | | |
| Metabolic acidosis with \( \uparrow \) AG, possible 2\(^{nd}\) respiratory alkalosis | Metabolic acidosis absent unless underlying precipitant leads to acidosis (e.g. lactic acidosis in MI) |
| If severe vomiting/dehydration there may be a metabolic alkalosis | |

| Urine | | |
| \( \uparrow \) ve for glucose and ketones | -ve for ketones unless there is starvation ketosis |
| Glycosuria | | |
Laboratory Testing: Ketones
The nitroprusside test for ketones identifies acetone and acetoacetate but does NOT detect β-hydroxybutyrate (BHB), the ketone most frequently in excess. This has two clinical consequences:
• Be wary of a patient with a clinical picture of DKA but negative serum or urinary ketones. These could be false negatives because of the presence of BHB.
• As DKA is treated, BHB is converted to acetone and acetoacetate. Serum or urinary ketones may therefore rise, falsely suggesting that the patient is worsening when in fact they are improving.

Table 12. Acute Complications of Diabetes Mellitus: Hyperglycemic Comatose States (continued)

<table>
<thead>
<tr>
<th>Diabetic Ketoacidosis (DKA)</th>
<th>Hyperosmolar Hyperglycemic State (HHS)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
</tr>
<tr>
<td>• ABCs are first priority</td>
<td>Same resuscitation and emergency measures as DKA</td>
</tr>
<tr>
<td>• Monitor degree of ketoacidosis with AG, not BG or serum ketone level</td>
<td>Rehydration</td>
</tr>
<tr>
<td>• Rehydration</td>
<td>– IV fluids: 1 L/h NS initially</td>
</tr>
<tr>
<td>– 1 L/h NS in first 2 h</td>
<td>– evaluate corrected serum Na⁺</td>
</tr>
<tr>
<td>– after 1st 2 L, 300-400 mL/h NS. Switch to 0.45% NaCl once euvolemic (continue NS if corrected sodium is falling faster than 3 mosm/kg water/h)</td>
<td>– if corrected serum Na⁺ high or normal, switch to 0.45% NaCl (4-14 mL/kg/h)</td>
</tr>
<tr>
<td>– once BG reaches 13.9 mmol/L then switch to D5W to maintain BG in the range of 12-14 mmol/L</td>
<td>– if corrected serum Na⁺ low, maintain NS (4-14 mL/kg/h)</td>
</tr>
<tr>
<td>• Insulin therapy</td>
<td>– when serum BG reaches 13.9 mmol/L switch to D5W</td>
</tr>
<tr>
<td>– critical to resolve acidosis, not hyperglycemia</td>
<td><strong>K⁺ replacement</strong></td>
</tr>
<tr>
<td>– do not use with hypokalemia (see below), until serum K⁺ is corrected to &gt;3.3 mmol/L</td>
<td>– less severe K⁺ depletion compared to DKA</td>
</tr>
<tr>
<td>– use only regular insulin (R)</td>
<td>– if serum K⁺ &lt;3.3 mmol/L, hold insulin and give 40 mEq/L K⁺ replacement</td>
</tr>
<tr>
<td>– maintain on 0.1 U/kg/h insulin R infusion</td>
<td>– if K⁺ is 3.3-5.0, give KCl 20-30 mEq/L IV fluid</td>
</tr>
<tr>
<td>– check serum glucose hourly</td>
<td>– if serum K⁺ ≥5.5 mmol/L, check K⁺ every 2 h</td>
</tr>
<tr>
<td>• K⁺ replacement</td>
<td>Search for precipitating event</td>
</tr>
<tr>
<td>– with insulin administration, hypokalemia may develop</td>
<td><strong>Insulin therapy</strong></td>
</tr>
<tr>
<td>– if serum K⁺ &lt;3.3 mmol/L, hold insulin and give 40 mEq/L K⁺ replacement</td>
<td>– use only regular insulin (R)</td>
</tr>
<tr>
<td>– when K⁺ 3.5-5.0 mmol/L add KCl 20-40 mEq/L IV fluid to keep K⁺ in the range of 3.5-5 mEq/L</td>
<td>– initially load 0.1 U/kg body weight insulin R bolus</td>
</tr>
<tr>
<td>• HCO₃⁻</td>
<td>– maintenance 0.1 U/kg/h insulin R infusion or IM</td>
</tr>
<tr>
<td>– if pH &lt;7.0 or if hypotension, arrhythmia, or coma is present</td>
<td>– check serum glucose hourly</td>
</tr>
<tr>
<td>with a pH of &lt;7.1 give HCO₃⁻ in 0.45% NaCl</td>
<td>– in general lower insulin requirement compared to DKA</td>
</tr>
<tr>
<td>– do not give if pH &gt;7.1 (risk of metabolic alkalosis)</td>
<td><strong>Prognosis</strong></td>
</tr>
<tr>
<td>– can give in case of life-threatening hyperkalemia</td>
<td>2.5% mortality in developed countries</td>
</tr>
<tr>
<td>± mannitol (for cerebral edema)</td>
<td>Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children)</td>
</tr>
</tbody>
</table>

**Macrovascular Complications**
- increased risk of CAD, ischemic stroke, and peripheral arterial disease secondary to accelerated atherosclerosis
- CAD (see Cardiology and Cardiac Surgery, C26)
  - risk of MI is 3-5x higher in those with DM compared to age-matched controls
  - CAD is the leading cause of death in type 2 DM
  - most patients with DM are considered “high risk” under the risk stratification for CAD (see Dyslipidemias, E2)
- ischemic stroke (see Neurology, N50)
  - risk of stroke is approximately 2.5x higher in those with DM
  - level of glycemia is both a risk factor for stroke and a predictor of a poorer outcome in patients who suffer a stroke
  - HbA1c level is a significant and independent predictor of the risk of stroke
- peripheral arterial disease (see Vascular Surgery, VS2)
  - manifested by intermittent claudication in lower extremities, intestinal angina, foot ulceration
  - risk of foot gangrene is 30x higher in those with DM compared to age-matched controls
  - risk of lower extremity amputation is 15x higher in those with DM
- treatment
  - tight blood pressure control (<130/80 mmHg); especially for stroke prevention
  - tight glycemic control in early DM without established CVD (refer to ACCORD, VADT, ADVANCE, DCCT, EDIC, UKPDS extension studies)
  - tight low density lipoprotein (LDL) cholesterol control (LDL ≤2.0 mmol/L)
  - ACEI or angiotensin receptor blocker in high-risk patients
  - smoking cessation

**Prognosis**
- 2-5% mortality in developed countries
- Serious morbidity from sepsis, hypokalemia, respiratory complications, thromboembolic complications, and cerebral edema (the latter in children)
- Overall mortality approaches 50% primarily because of the older patient population and underlying etiology/precipitant

Average fluid loss runs at 3-6 L in DKA, and 8-10 L in HHS
Microvascular Complications

DIABETIC RETINOPATHY (see Ophthalmology, OP35 for a more detailed description)

Epidemiology
- type 1 DM: 25% affected at 5 yr, 100% at 20 yr
- type 2 DM: 25% affected at diagnosis, 60% at 20 yr
- leading cause of blindness in North America between the ages of 20-74
- most important factor is disease duration

Clinical Features
- nonproliferative
- preproliferative
- proliferative

Treatment and Prevention
- tight glycemic control (delays onset, decreases progression), tight lipid control, manage HTN, smoking cessation
- ophthalmological treatments available – see Ophthalmology, OP36 for more details
- annual follow-up visits with an optometrist or ophthalmologist examination through dilated pupils whether symptomatic or not (immediate referral after diagnosis of type 2 DM; 5 yr after diagnosis of type 1 DM)
- interval for follow-up should be tailored to severity of retinopathy

DIABETIC NEPHROPATHY (see Nephrology, NP30 for a more detailed description)

Epidemiology
- DM-induced renal failure is the most common cause of renal failure in North America
- 20-40% of persons with type 1 DM (after 5-10 yr) and 4-20% with type 2 DM have progressive nephropathy

Screening
- serum creatinine
- random urine test for albumin to creatinine ratio (ACR) plus urine dipstick test for all type 2 DM patients at diagnosis, then annually, and for postpubertal type 1 DM patients with ≥5 yr duration of DM

Treatment and Prevention
- appropriate glycemic control
- appropriate blood pressure control (<130/80 mmHg)
- use either ACEI or ARB (often used first line for their CVD protection)
- limit use of nephrotoxic drugs and dyes

DIABETIC NEUROPATHY

Epidemiology
- approximately 50% of patients within 10 yr of onset of type 1 DM and type 2 DM

Pathophysiology
- can have peripheral sensory neuropathy, motor neuropathy, or autonomic neuropathy
- mechanism poorly understood
- acute cranial nerve palsies and diabetic amyotrophy are thought to be due to ischemic infarction of peripheral nerve
- the more common motor and sensory neuropathies are thought to be related to metabolic or osmotic toxicity secondary to increased sorbitol and/or decreased myoinositol (possible mechanisms include accumulation of advanced glycation endproducts [AGE], oxidative stress, protein kinase C, nerve growth factor deficiency)

Screening
- 128 Hz tuning fork or 10 g monofilament at diagnosis and annually in people with type 2 DM and after 5 yr duration of type 1 DM
Clinical Features

Table 13. Clinical Presentation of Diabetic Neuropathies

<table>
<thead>
<tr>
<th>Peripheral Sensory Neuropathy</th>
<th>Motor Neuropathy</th>
<th>Autonomic Neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesias (tingling, itching), neuropathic pain, radicular pain, numbness, decreased tactile sensation</td>
<td>Less common than sensory neuropathy</td>
<td>Postural hypotension, tachycardia, decreased cardiovascular response to Valsalva maneuver</td>
</tr>
<tr>
<td>Bilateral and symmetric with decreased perception of vibration and pain/temperature; especially true in the lower extremities but may also be present in the hands</td>
<td>Delayed motor nerve conduction and muscle weakness/atrophy</td>
<td>Gastroparesis and alternating diarrhea and constipation</td>
</tr>
<tr>
<td>Decreased ankle reflex</td>
<td>May involve one nerve trunk (mononeuropathy) or more (mononeuritis multiplex)</td>
<td>Urinary retention and erectile dysfunction</td>
</tr>
<tr>
<td>Symptoms may first occur in entrapment syndromes e.g. carpal tunnel</td>
<td>Some of the motor neuropathies spontaneously resolve after 6-8 wk</td>
<td></td>
</tr>
<tr>
<td>May result in neuropathic ulceration of foot</td>
<td>Reversible CN palsies: III (ptosis/ophthalmoplegia, pupil sparing), VI (inability to laterally deviate eye), and VII (Bell’s palsy)</td>
<td></td>
</tr>
</tbody>
</table>

Treatment and Management
- tight glycemic control
- for neuropathic pain syndromes: tricyclic antidepressants (e.g. amitriptyline), pregabalin, duloxetine, anti-epileptics (e.g. carbamazepine, gabapentin), and capsaicin
- foot care education
- Jobst® fitted stocking and tilting of head of bed may decrease symptoms of orthostatic hypotension
- treat gastroparesis with domperidone and/or metoclopramide (dopamine antagonists), medical, mechanical, and surgical treatment for erectile dysfunction (see Urology, U30)

Other Complications

Dermatologic
- diabetic dermopathy: atrophic brown spots commonly in pre-tibial region known as “skin spots”, secondary to increased glycosylation of tissue proteins or vasculopathy
- eruptive xanthomas secondary to increased triglycerides
- necrobiosis lipoidica diabeticorum: rare complication characterized by thinning skin over the hands

Bone and Joint Disease
- juvenile cheiroarthropathy: chronic stiffness of hand caused by contracture of skin over joints secondary to glycosylated collagen and other connective tissue proteins
- Dupuytren’s contracture
- bone demineralization: bone density 10-20% below normal
- adhesive capsulitis (“frozen shoulder”)

Cataracts
- subcapsular and senile cataracts secondary to glycosylated lens protein or increased sorbitol causing osmotic change and fibrosis

Infections
- see Infectious Diseases, ID15

Hypoglycemia (BG <4.0 mmol/L or 72 mg/dL)

Etiology and Pathophysiology
- hypoglycemia occurs most frequently in people with DM receiving insulin or certain antihyperglycemic therapies (insulin secretagogues)
- in people without DM, care must be taken to distinguish fasting from post-prandial hypoglycemia as each invokes separate differential diagnoses

Other Players in Glucose Homeostasis
- Glucagon
- Epinephrine
- Cortisol
- Growth hormone

C-Peptide
- A short peptide released into the circulation when proinsulin is cleaved into insulin
Table 14. Common Causes of Hypoglycemia

<table>
<thead>
<tr>
<th>Fasting Post-Prandial (Nonfasting, Reactive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperinsulinism Without Hyperinsulinism</td>
</tr>
<tr>
<td>• Exogenous insulin</td>
</tr>
<tr>
<td>• Sulfonylurea or meglitinide reaction</td>
</tr>
<tr>
<td>• Autoimmune hypoglycemia (autoantibodies to insulin or insulin receptor)</td>
</tr>
<tr>
<td>• Pentamidine</td>
</tr>
<tr>
<td>• Pancreatic β cell tumour – insulinoma</td>
</tr>
<tr>
<td>• Severe hepatic dysfunction</td>
</tr>
<tr>
<td>• Chronic renal insufficiency</td>
</tr>
<tr>
<td>• Alcohol use</td>
</tr>
<tr>
<td>• Non-pancreatic tumours</td>
</tr>
<tr>
<td>• Inborn error of carbohydrate metabolism, glycogen storage disease, gluconeogenic enzyme deficiency</td>
</tr>
<tr>
<td>• Alimentary</td>
</tr>
<tr>
<td>• Functional</td>
</tr>
<tr>
<td>• Noninsulinoma pancreatogenous hypoglycemic syndrome</td>
</tr>
<tr>
<td>• Occult DM</td>
</tr>
<tr>
<td>• Leucine sensitivity</td>
</tr>
<tr>
<td>• Hereditary fructose intolerance</td>
</tr>
<tr>
<td>• Galactosemia</td>
</tr>
<tr>
<td>• Newborn infant of diabetic mother</td>
</tr>
</tbody>
</table>

Clinical Features
- Whipple’s triad
  1. serum glucose <2.5 mmol/L in males and <2.2 mmol/L in females
  2. neuroglycopenic symptoms
  3. rapid relief provided by administration of glucose
- adrenergic symptoms (typically occur first; caused by autonomic nervous system activity)
  - palpitations, sweating, anxiety, tremor, tachycardia
- neuroglycopenic symptoms (caused by decreased activity of CNS)
  - dizziness, headache, clouding of vision, mental dullness, fatigue, confusion, seizures, coma

Investigations
do-electrolytes, creatinine, LFTs, drugs/toxins, cortisol
-if concerned about possible insulinoma
  - blood work to be drawn when patient is hypoglycemic (e.g. during hospitalized 72-h fast) for glucose, serum ketones, insulin, pro-insulin, C-peptide, insulin antibodies

Treatment
- for fasting hypoglycemia, must treat underlying cause
- for post-prandial (reactive) hypoglycemia, frequent small feeds
- see Emergency Medicine, ER35
- treatment of hypoglycemic episode in the unconscious patient or patient NPO
  - D50W 50 mL (1 ampule) IV or 1 mg glucagon SC (if no IV available)
  - may need ongoing glucose infusion once BG >5 mmol/L

Metabolic Syndrome
- several definitions exist
- postulated syndrome related to insulin resistance associated with hyperglycemia, hyperinsulinemia, HTN, central obesity, and dyslipidemia
- obesity aggravates extent of insulin resistance
- complications include DM, atherosclerosis, CAD, MI, and stroke
- women with PCOS are at increased risk for developing insulin resistance, hyperlipidemia, and metabolic syndrome
- not to be confused with syndrome X related to angina pectoris with normal coronary arteries (Prinzmetal angina)

Obesity
- see Family Medicine, FM7
**Pituitary Gland**

**Pituitary Hormones**

- **Hypothalamic Control of Pituitary**
  - trophic and inhibitory factors control the release of pituitary hormones
  - most hormones are primarily under trophic stimulation except prolactin which is primarily under inhibitory control by dopamine, as well as GH and TSH which are inhibited by SS (somatostatin)
  - transection of the pituitary stalk (i.e. dissociation of hypothalamus and pituitary) leads to pituitary hypersecretion of prolactin and hyposecretion of all remaining hormones

- **Anterior Pituitary Hormones**
  - growth hormone (GH), luteinizing hormone (LH), follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), adrenocorticotropic hormone (ACTH), and prolactin (PRL)

- **Posterior Pituitary (Hypothalamic) Hormones**
  - antidiuretic hormone (ADH) and oxytocin
  - peptides synthesized in the supraoptic and paraventricular nuclei of the hypothalamus
  - although ADH and oxytocin are produced in the hypothalamus these hormones are stored and released from the posterior pituitary

**Table 15. The Physiology and Action of Pituitary Hormones**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACTH</td>
<td>Stimulates growth of adrenal cortex and secretion of its hormones</td>
<td>Polypeptide</td>
<td>Dexamethasone, Cortisol</td>
<td>CRH, Metyrapone, Insulin-induced hypoglycemia, Vasopressin, Fever, pain, stress</td>
</tr>
<tr>
<td>GH</td>
<td>Needed for linear growth, IGF-1 stimulates growth of bone and cartilage</td>
<td>Polypeptide, Serum GH undetectable for most of the day and suppressed after meals high in glucose, Sustained rise during sleep</td>
<td>Glucose challenge, Hypoglycemia, Somatostatin, Dopa D2 receptor agonists, IGF-1 (long-loop)</td>
<td>GHHR, Insulin-induced hypoglycemia, Exercise, REM sleep, Arginine, clonidine, propranolol, L-dopa</td>
</tr>
</tbody>
</table>
Table 15. The Physiology and Action of Pituitary Hormones (continued)

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Function</th>
<th>Physiology</th>
<th>Inhibitory Stimulus</th>
<th>Secretory Stimulus</th>
</tr>
</thead>
<tbody>
<tr>
<td>LH/FSH</td>
<td>Stimulate gonads via cAMP</td>
<td>Polypeptide</td>
<td>Estrogen, Progesterone</td>
<td>Pulsatile GnRH</td>
</tr>
<tr>
<td></td>
<td>Ovary:</td>
<td>Glycoproteins (similar α subunit as TSH and hCG)</td>
<td>Testosterone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– LH: production of androgens (thecal cells) which are converted to estrogens (granulosa cells); induces luteinization in follicles</td>
<td>Secreted in pulsatile fashion</td>
<td>Inhibin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>– FSH: growth of granulosa cells in ovarian follicle; controls estrogen formation</td>
<td></td>
<td>Continuous (i.e. non-pulsatile) GnRH infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testes:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– LH: production of testosterone (Leydig cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>– FSH: production of spermatozoa (Sertoli cells)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>Promotes milk production</td>
<td>Polypeptide</td>
<td>Dopamine</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td>Inhibits GnRH secretion</td>
<td>Episodic secretion</td>
<td></td>
<td>Stress, hypoglycemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pregnancy, breastfeeding</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mid-menstrual cycle</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Sexual activity</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TRH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Drugs: psychotropics, antihypertensives, dopamine antagonists, opiates, high dose estrogen</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>Stimulates growth of thyroid and secretion of T3 and T4 via cAMP</td>
<td>Glycoprotein</td>
<td>Circulating thyroid hormones (T3, T4)</td>
<td>TRH</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Opiates, dopamine</td>
<td>Epinephrine</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prostaglandins</td>
</tr>
<tr>
<td>ADH</td>
<td>Acts at renal collecting ducts on V2 receptors to cause insertion of aquaporin channels and increases water reabsorption thereby concentrating urine</td>
<td>Octapeptide</td>
<td>↓ serum osmolality</td>
<td>Hypovolemia or ↓ effective circulatory volume</td>
</tr>
<tr>
<td></td>
<td>Secreted by posterior pituitary</td>
<td>Osmoreceptors in hypothalamus detect serum osmolality</td>
<td>↑ serum osmolality</td>
<td>↑ serum osmolality</td>
</tr>
<tr>
<td></td>
<td>Contracted plasma volume detected by baroreceptors is a more potent stimulus than ↓ osmolality</td>
<td></td>
<td>Stress, pain, fever, paraneoplastic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lung or brain pathology</td>
<td></td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Causes uterine contraction</td>
<td>Not a peptide</td>
<td>EtOH</td>
<td>Suckling</td>
</tr>
<tr>
<td></td>
<td>Breast milk secretion</td>
<td>Secreted by posterior pituitary</td>
<td></td>
<td>Distention of female genital tract during labor via stretch receptors</td>
</tr>
</tbody>
</table>

**Growth Hormone**

**GH DEFICIENCY**
- cause of short stature in children (see Pediatrics, P27)
- controversial significance in adults; often not clinically apparent, may present as fatigue

**GH EXCESS**
- in children (before epiphyseal fusion) leads to gigantism
- in adults (after epiphyseal fusion) leads to acromegaly

**Etiology**
- GH secreting pituitary adenoma, carcinoid or pancreatic islet tumours secreting ectopic GHRH resulting in excess GH

**Pathophysiology**
- normally GH is a catabolic hormone that acts to increase blood glucose levels
- in growth hormone excess states secretion remains pulsatile but there is loss of hypoglycemic stimulation, glucose suppression, and the nocturnal surge
- proliferation of bone, cartilage, soft tissues, organomegaly
- insulin resistance and IGT

**Clinical Features**
- enlargement of hands and feet, coarsening of facial features, thickening of calvarium, prognathism, thickening of skin, increased sebum production, sweating, acne, sebaceous cysts, fibromata mollusca, acanthosis nigricans, arthralgia, carpal tunnel syndrome, degenerative osteoarthritis, barrel chest, thyromegaly, renal calculi, HTN, cardiomyopathy, obstructive sleep apnea, colonic polyps, erectile dysfunction, menstrual irregularities, and DM

**Risks Associated with GH Excess**
- Cardiac disease (e.g. CAD, cardiomegaly, cardiomyopathy) in 1/3 of patients, with a doubling of risk of death from cardiac disease
- HTN in 1/3 of patients
- Risk of cancer (particularly GI) increased 2-fold to 3-fold

**Signs and Symptoms of Acromegaly**
- ABCDEF
  - Arthralgia/Arthritis
  - Blood pressure raised
  - Carpal tunnel syndrome
  - DM
  - Enlarged organs
  - Field defect (visual)
Investigations
- elevated serum insulin-like growth factor-1 (IGF-1) is usually the first line diagnostic test
- glucose suppression test is the most specific test (75 g of glucose PO suppresses GH levels in healthy individuals but not in patients with acromegaly)
- CT, MRI, or skull x-rays may show cortical thickening, enlargement of the frontal sinuses, and enlargement and erosion of the sella turcica
- MRI of the sella turcica is needed to look for a tumour

Treatment
- surgery, octreotide (somatostatin analogue), dopamine agonist (bromocriptine/cabergoline), growth hormone receptor antagonist (pegvisomant), radiation

Prolactin

HYPERPROLACTINEMIA

Etiology
- pregnancy and breastfeeding
- prolactinoma: most common pituitary adenoma (prolactin-secreting tumours may be induced by estrogens and grow during pregnancy)
- pituitary masses with pituitary stalk compression causing reduced dopamine inhibition of prolactin release
- primary hypothyroidism (increased TRH)
- decreased clearance due to chronic renal failure or severe liver disease (prolactin is metabolized by both the kidney and liver)
- medications with anti-dopaminergic properties are a common cause of high prolactin levels: antipsychotics (common), antidepressants, anti-hypertensives, anti-migraine agents (triptans/ergotamines), bowel motility agents (metoclopramide/domperidone), H2-blockers (ranitidine)
- macroprolactinemia (high molecular weight prolactin also known as big big prolactin)

Clinical Features
- galactorrhea (secretion of breast milk in women and, in rare cases, men), infertility, hypogonadism, amenorrhea, erectile dysfunction

Investigations
- serum PRL, TSH, liver enzyme tests, creatinine
- MRI of the sella turcica

Treatment
- long-acting dopamine agonist: bromocriptine, cabergoline, or quinagolide (Norprolac®)
- surgery ± radiation (rare)
- prolactin-secreting tumours are very slow-growing and sometimes require no treatment
- if medication-induced, consider stopping medication if possible
- in certain cases if microprolactinoma and not planning on becoming pregnant, may consider OCP

Thyroid Stimulating Hormone

• see Thyroid, E20

Adrenocorticotropic Hormone

• see Adrenal Cortex, E29

Luteinizing Hormone and Follicle Stimulating Hormone

HYPOGONADOTROPIC HYPOGONADISM

Clinical Features
- hypogonadism, amenorrhea, erectile dysfunction (see Urology, U30), loss of body hair, fine skin, testicular atrophy, failure of pubertal development

Treatment
- Pergonal® (combined FSH/LH hormone therapy), hCG, rFSH, or pulsatile GnRH analogue if fertility desired
- symptomatic treatment with estrogen/testosterone

Approach to Nipple Discharge
- Differentiate between galactorrhea (fat droplets present) versus breast discharge (usually unilateral, may be bloody or serous)
- If galactorrhea, determine if physiologic (e.g. pregnancy, lactation, stress) versus pathologic
- If abnormal breast discharge, must rule out a breast malignancy
HYPERGONADOTROPIC HYPOGONADISM
- 2º hypersecretion in gonadal failure (e.g. in menopause)

Antidiuretic Hormone

DIABETES INSIPIDUS

Definition
- disorder of ineffective ADH (decreased production or peripheral resistance) resulting in passage of large volumes of dilute urine

Etiology and Pathophysiology
- central DI: insufficient ADH due to pituitary surgery, tumours, idiopathic/autoimmune, stalk lesion, histiocytosis X, trauma, familial central DI
- nephrogenic DI: collecting tubules in kidneys resistant to ADH due to drugs (e.g. lithium), hypercalcemia, hypokalemia, chronic renal disease, hereditary nephrogenic DI
- psychogenic polydipsia and osmotic diuresis must be ruled out

Clinical Features
- passage of large volumes of dilute urine, polydipsia, and dehydration; hypernatremia can develop with inadequate water consumption or secondary to an impaired thirst mechanism

Diagnostic Criteria
- fluid deprivation will differentiate true DI (high urine output persists, urine osmolality < plasma osmolality) from psychogenic DI (psychogenic polydipsia)
- response to exogenous ADH (DDAVP) will distinguish central from nephrogenic DI

Treatment
- DDAVP/vasopressin for central DI
- chlorpropamide, clofibrate, thiazides, NSAIDs, or carbamazepine as second line or for partial DI
- nephrogenic DI treated with solute restriction NSAIDs and thiazide diuretics; DDAVP (if partial)

SYNDROME OF INAPPROPRIATE ADH SECRETION

Diagnostic Criteria
- hyponatremia with corresponding plasma hypo-osmolality, urine sodium concentration above 40 mEq/L, urine less than maximally diluted (>100 mOsm/kg), euvolemia (edema absent), and absence of adrenal, renal, or thyroid insufficiency

Etiology and Pathophysiology
- stress (pain, nausea, post-surgical)
- malignancy (lung, pancreas, lymphoma)
- CNS disease (inflammatory, hemorrhage, tumour, Guillain-Barré syndrome)
- respiratory disease (TB, pneumonia, empyema)
- drugs (SSRIs, vincristine, chlorpropamide, cyclophosphamide, carbamazepine, nicotine, morphine, DDAVP, oxytocin)

Treatment
- treat underlying cause, fluid restriction (800-1000 mL/day), vasopressin receptor antagonists (e.g. tolvaptan, conivaptan), and demeclocycline (antibiotic with anti-ADH properties, rarely-used) fluoroecortisone, furosemide

Pituitary Pathology

PITUITARY ADENOMA (see Neurosurgery, NS19)

Clinical Features
- local mass effects
  - visual field defects (bitemporal hemianopsia due to compression of the optic chiasm), diplopia (due to oculomotor nerve palsies), headaches; increased ICP is rare
  - hypofunction
    - hypopituitarism
  - hyperfunction
    - PRL (galactorrhea), GH (acromegaly in adults, gigantism in children), ACTH (Cushing’s disease = Cushing’s syndrome caused by a pituitary tumour)
    - tumours secreting LH, FSH, and TSH are rare

Important Deficiencies to Recognize
- Adrenal insufficiency
- Hypothyroidism

Concurrent adrenal insufficiency and hypothyroidism should be treated with glucocorticoids first and then with thyroid hormone to avoid adrenal crisis.
Investigations
- radiological evaluation (MRI is imaging procedure of choice)
- formal visual field testing
- hypothalamic-pituitary hormonal function

HYPOPITUITARISM

**Etiology (The Eight Is)**
- Invasive
  - pituitary tumours, craniopharyngioma, cysts (Rathke's cleft, arachnoid, or dermoid), metastases
- Infarction/hemorrhage
  - Sheehan's syndrome (pituitary infarction due to excessive post-partum blood loss and hypovolemic shock)
  - pituitary apoplexy (acute hemorrhage/infarction of a pituitary tumour; presents with sudden loss of pituitary hormones, severe headache, and altered level of consciousness; can be fatal if not recognized and treated early)
- Infiltrative/inflammatory
  - sarcoidosis, hemochromatosis, histiocytosis
- Infectious
  - syphilis, TB, fungal (histoplasmosis), parasitic (toxoplasmosis)
- Injury
  - severe head trauma
- Immunologic
  - autoimmune destruction
- Iatrogenic
  - following surgery or radiation
- Idiopathic
  - familial forms, congenital midline defects

**Investigations**
- triple bolus test
  - stimulates release of all anterior pituitary hormones in normal individuals
  - rapid sequence of IV infusion of insulin, GnRH, and TRH
  - insulin (usual dose 0.1 unit/kg of human regular insulin) → hypoglycemia → increased GH and ACTH/cortisol
  - GnRH (100 µg IV push) → increased LH and FSH
  - TRH (200 µg IV push over 120 s) → increased TSH and PRL (no longer available in Canada)

**Thyroid**

**Thyroid Hormones**

![Figure 8. Thyroid hormone synthesis](https://example.com/image.jpg)

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DIT = diiodotyrosine; L = lysosome; MIT = monoiodotyrosine; TG = thyroglobulin; T3 = triiodothyronine; T4 = thyroxine (tetraiodothyronine); TP = thyroid peroxidase enzyme

Order they are usually lost with compression by a mass:
“Go Look For The Adenoma Please”
GH, LH, FSH, TSH, ACTH, PRL + posterior pituitary hormones: ADH and oxytocin
Synthetic Function of Thyroid Gland

- the synthesis of thyroid hormones T₄ (thyroxine) and T₃ (triiodothyronine) by the thyroid gland involves trapping and oxidation of iodide, iodination of thyroglobulin, and release of T₃ and T₄
- free T₄ (0.03%) and free T₃ (0.3%) represent the hormonally active fraction of thyroid hormones
  - the remaining fraction is bound to thyroxine binding globulin (TBG) and albumin and is biologically inactive
- T₄ is more biologically active (3-8x more potent), but T₄ has a longer half-life
- 83% of T₄ is converted to T₃ or reverse T₃ (rT₃) in the periphery by deiodinases
- rT₃ is metabolically inactive but produced in times of stress to decrease metabolic activity
- most of the plasma T₄ pool is derived from the peripheral conversion of T₃
- calcitonin, a peptide hormone, is also produced in the thyroid, by the parafollicular cells or C cells
  - it functions by inhibiting osteoclast activity and increasing renal calcium excretion

Role of Thyroid Hormones

- thyroid hormones act primarily through modifying gene transcription by binding to nuclear receptors
- action of these hormones is diffuse, effecting nearly every organ system
- they produce an increase in basal metabolic rate including: increased Na⁺/K⁺ ATPase activity, increased O₂ consumption, increased respiration, heat generation, and increased cardiovascular activity
- they also play crucial role during fetal life in both neurological and somatic development

Regulation of Thyroid Function

- extrathyroid
  - stimulation of thyroid by TSH, epinephrine, prostaglandins (cAMP stimulators)
  - T₃ negatively feeds back on anterior pituitary to inhibit TSH and on hypothalamus to inhibit TRH
- intrathyroid (autoregulation)
  - synthesis (Wolff-Chaikoff effect, Jod-Basedow effect)
  - there is varying thyroid sensitivity to TSH in response to iodide availability
  - increased ratio of T₃ to T₄ in iodide deficiency
  - increased activity of peripheral 5’ deiodinase in hypothyroidism increases T₃ production despite low T₄ levels

Tests of Thyroid Function and Structure

TSH

- sensitive TSH (sTSH) is the best test for assessing thyroid function
- hyperthyroidism
  - primary: TSH is low because of negative feedback from increased levels of circulating T₃ and T₄
  - secondary: increased TSH results in increased T₃ and T₄
- hypothyroidism
  - primary: increased TSH (most sensitive test) because of less negative feedback from T₃ and T₄
  - secondary: TSH is low or normal with variable response to TRH depending on the site of the lesion (pituitary or hypothalamic)

Free T₃ and Free T₄

- standard assessment of thyroid function measures TSH and if necessary free T₄. Free T₃ should only be measured in the small subset of patients with hyperthyroidism and suspected T₃ toxicity. TSH would be suppressed, free T₄ normal, and free T₃ elevated

Thyroid Autoantibodies

- anti-thyroglobulin antibodies (TgAb), anti-thyroid peroxidase antibodies (TPOAb), anti-TSH receptor antibodies (TRAb) of the blocking variety
  - increased in Hashimoto’s disease; normal variant in 10-20% of individuals
  - anti-TSH receptor antibodies (TRAb) of the stimulating variety are also referred to as thyroid stimulating immunoglobulins (TSI)
  - increased in Graves’ disease

Plasma Thyroglobulin

- used to monitor for residual thyroid tissue post-thyroidectomy, e.g. tumour marker for thyroid cancer recurrence
- normal or elevated levels may suggest persistent, recurrent, or metastatic disease

Serum Calcitonin

- not routinely done to investigate thyroid nodules
- ordered if suspicion of medullary thyroid carcinoma or family history of MEN IIa or IIb syndromes
  - used to monitor for residual or recurrent medullary thyroid cancer

Patterns of Hormone Levels

<table>
<thead>
<tr>
<th>TSH T3 T4</th>
<th>1° Hyper</th>
<th>2° Hyper</th>
<th>1° Hypo</th>
<th>2° Hypo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1° Hyper</td>
<td>T</td>
<td>T</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>2° Hyper</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>1° Hypo</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>2° Hypo</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>
Thyroid Imaging/Scans
- normal gland size 15-20 g (estimated by palpation)
- thyroid U/S
  - to measure size of gland, solid vs. cystic nodule, facilitate fine needle aspirate biopsy (FNAB)
- radioactive iodine scan (Technetium-99)
  - test of structure: order if there is a thyroid nodule and patient is hyperthyroid with low TSH
  - differentiates between hot (functioning → excess thyroid hormone production) and cold (non-functioning) nodules
  - hot nodule → very low chance malignancy; treat hyperthyroidism
  - cold nodule → ~5% chance malignancy; further workup required (U/S and FNAB)
- radioactive iodine uptake (RAIU)
  - test of function: order if patient is thyrotoxic
  - RAIU measures the turnover of iodine by thyroid gland in vivo
  - if ↑ uptake (i.e. incorporated) → gland is overactive (hyperthyroidism)
  - if ↓ uptake (i.e. not incorporated) → gland is leaking thyroid hormone (e.g. thyroiditis), exogenous thyroid hormone use, or excess iodine intake (e.g. amiodarone or contrast dye, which has high iodine content)
- see Figure 9, Approach to the Evaluation of a Thyroid Nodule, E29 for further information regarding the utility of these scans

Thyroid Biopsy
- fine needle aspiration (FNA) for cytology
- differentiates between benign and malignant disease
- best done under U/S guidance
- accuracy decreased if nodule is greater than 50% cystic, or if nodule located posteriorly in the gland

Table 16. Summary of Diagnostic Testing in Hyperthyroidism and Hypothyroidism

<table>
<thead>
<tr>
<th></th>
<th>Hyperthyroidism</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH</td>
<td>• Decreased in 1° hyperthyroidism</td>
<td>• Increased in 1° hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Increased in 2° hyperthyroidism</td>
<td>• Decreased in 2° hypothyroidism</td>
</tr>
<tr>
<td>Free T4</td>
<td>• Increased in 1° hyperthyroidism</td>
<td>• Decreased in 1° hypothyroidism</td>
</tr>
<tr>
<td></td>
<td>• Increased in 2° hyperthyroidism</td>
<td>• Decreased in 2° hypothyroidism</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Graves': thyroid stimulating Ig (TSI)</td>
<td>Hashimoto’s: antithyroid peroxidase (TPO)</td>
</tr>
<tr>
<td>RAIU</td>
<td>• Increased uptake</td>
<td>• Decreased uptake</td>
</tr>
<tr>
<td></td>
<td>• Graves’</td>
<td>• Subacute thyroiditis</td>
</tr>
<tr>
<td></td>
<td>• Toxic multinodular goitre</td>
<td>• Recent iodine load</td>
</tr>
<tr>
<td></td>
<td>• Toxic adenoma</td>
<td>• Exogenous thyroid hormone</td>
</tr>
<tr>
<td>Radioisotope</td>
<td>Graves': homogenous diffuse uptake</td>
<td></td>
</tr>
<tr>
<td>Thyroid Scan</td>
<td>Multinodular goitre: heterogeneous uptake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Toxic adenoma: single intense area of</td>
<td></td>
</tr>
<tr>
<td></td>
<td>uptake with suppression elsewhere</td>
<td></td>
</tr>
</tbody>
</table>

Thyrotoxicosis

Definition
- clinical, physiological, and biochemical findings in response to elevated thyroid hormone

Epidemiology
- 1% of general population have hyperthyroidism
- F:M = 5:1

Etiology and Pathophysiology

Table 17. Differential Diagnosis of Thyrotoxicosis

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free T4/T3</th>
<th>Thyroid Antibodies</th>
<th>RAIU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>HYPERTHYROIDISM</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Graves’ Disease</td>
<td>Decreased</td>
<td>Increased</td>
<td>TSI</td>
<td>Increased</td>
<td>Heterogeneous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodular Goitre</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Heterogeneous uptake on scan</td>
</tr>
<tr>
<td>Toxic Nodule</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td>Intense uptake in hot nodule in the rest of the gland</td>
</tr>
<tr>
<td>THYROIDITIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute, Silent, Postpartum</td>
<td>Decreased</td>
<td>Increased</td>
<td>Up to 50% of cases</td>
<td>Decreased becomes increased once entering hypothyroid phase, when TSH rises</td>
<td>In classical subacute painful thyroiditis, ESR increased</td>
</tr>
</tbody>
</table>

Caution with Amiodarone
Amiodarone-Induced Hypothyroidism (AIH): AIH occurs more often in iodine-sufficient areas, and is more common in populations with a higher prevalence of autoimmune thyroid disease, such as women and the elderly. AIH can also occur in patients without pre-existing thyroid dysfunction.

Amiodarone-Induced Thyrotoxicosis (AIT): AIT occurs more often in iodine-deficient areas. It may occur in patients with pre-existing thyroid deficiencies, as an iodine load on an already dysfunctional thyroid may result in excessive thyroid hormone synthesis and release. AIT may also occur in patients without thyroid abnormalities through a cytotoxic mechanism that results in leakage of thyroid hormone into the systemic circulation.

Signs and Symptoms of HYPERthyroidism
- Tremor
- Heart rate up
- Yawning (fatigued)
- Restlessness
- Oligomenorrhea/amenorrhea
- Intolerance to heat
- Diarrhea
- Irritability
- Sweating
- Muscle wasting/weight loss

Common Etiologies

<table>
<thead>
<tr>
<th>Thyrotoxicosis</th>
<th>Hypothyroidism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Graves’ Disease</td>
<td>Hashimoto’s</td>
</tr>
<tr>
<td>Toxic Nodular Goitre</td>
<td>Congenital</td>
</tr>
<tr>
<td>Toxic Nodule</td>
<td>Iatrogenic (thionamides, radioactive iodine, surgery)</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Hypothyroid phase of thyroiditis</td>
</tr>
</tbody>
</table>
Table 17. Differential Diagnosis of Thyrotoxicosis (continued)

<table>
<thead>
<tr>
<th>Disorder</th>
<th>TSH</th>
<th>Free $\text{T}_4$/T3</th>
<th>Thyroid Antibodies</th>
<th>RAIU</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EXTRATHYROIDAL SOURCES OF THYROID HORMONE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endogenous (struma ovariae, ovarian teratoma, metastatic follicular carcinoma)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>Exogenous (drugs)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Decreased</td>
<td></td>
</tr>
<tr>
<td>(T4 would be decreased if taking T3)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EXCESSIVE THYROID STIMULATION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pituitary thyrotophoma</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Pituitary thyroid hormone receptor resistance</td>
<td>Increased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td></td>
</tr>
<tr>
<td>Increased hCG (e.g. pregnancy)</td>
<td>Decreased</td>
<td>Increased</td>
<td>None</td>
<td>Increased</td>
<td><strong>DO NOT DO THIS TEST IN PREGNANCY</strong></td>
</tr>
</tbody>
</table>

Clinical Features

Table 18. Clinical Features of Thyrotoxicosis

| General                                | Fatigue, heat intolerance, irritability, fine tremor |
| CVS                                    | Tachycardia, atrial fibrillation, palpitations       |
| GI                                     | Weight loss with increased appetite, thirst, increased frequency of bowel movements (hyperdefecation) |
| Neurology                              | Proximal muscle weakness, hypokalemic periodic paralysis (more common in Asians) |
| GU                                     | Oligomenorrhea, amenorrhea, decreased fertility      |
| Dermatology                            | Fine hair, skin moist and warm, vitiligo, soft nails with onycholysis (Plummer's nails), palmar erythema, pruritis   |
|                                         | Graves' disease: clubbing (acropachy), pretibial myxedema (rare) |
| MSK                                    | Decreased bone mass, proximal muscle weakness        |
| Hematology                             | Graves' disease: leukopenia, lymphocytosis, splenomegaly, lymphadenopathy (occasionally) |
| Eye                                    | Graves' disease: lid lag, retraction, proptosis, diplopia, decreased acuity, puffiness, conjunctival injection |

Treatment
- thionamides: PTU or MMI; MMI recommended (except in first trimester pregnancy)
- $\beta$-blockers for symptom control
- radioactive iodine thyroid ablation for Graves' disease
- surgery in the form of hemi, sub-total, or complete thyroidectomy

Graves' Disease

Definition
- an autoimmune disorder characterized by autoantibodies to the TSH receptor that leads to hyperthyroidism

Epidemiology
- most common cause of thyrotoxicosis
- occurs at any age with peak in 3rd and 4th decade
- $F:M = 7:1$, 1.5-2% of U.S. women
- familial predisposition: 15% of patients have a close family member with Graves' disease and 50% have family members with positive circulating antibodies
- association with HLA B8 and DR3
- may be associated with other inherited autoimmune disorders (e.g. pernicious anemia, Hashimoto's disease)

Etiology and Pathophysiology
- autoimmune disorder due to a defect in T-suppressor cells
- B lymphocytes produce TSI that binds and stimulates the TSH receptor and stimulates the thyroid gland
- immune response can be triggered by postpartum state, iodine excess, lithium therapy, viral or bacterial infections, glucocorticoid withdrawal
- ophthalmopathy (thyroid associated orbitopathy) a result of increased tissue volume due to inflammation and accumulation of glycosaminoglycans, stimulated by TSI, that increase osmotic pressure within the orbit; this leads to fluid accumulation and displacement of the eye ball forward
- dermopathy may be related to cutaneous glycosaminoglycan deposition

Graves' Ophthalmopathy

NO SPECS (in order of changes usually)
- No signs
- Only signs: lid lag, lid retraction
- Soft tissue: periocular puffiness, conjunctival injection, chemosis
- Proptosis/exophthalmos
- Extraocular (diplopia)
- Corneal abrasions (since unable to close eyes)
- Sight loss
Clinical Features
• signs and symptoms of thyrotoxicosis
  - diffuse thyroid goitre ± thyroid bruit secondary to increased blood flow through the gland
  - ophthalmopathy: proptosis, diplopia, conjunctival injection, corneal abrasions, periorbital puffiness, lid lag, decreased visual acuity if Graves’ (plus signs of hyperthyroidism: lid retraction, characteristic stare)
  - dermopathy (rare): pretibial myxedema (thickening of dermis that manifests as non-pitting edema)
  - acropachy: clubbing and thickening of distal phalanges

Investigations
• low TSH
• increased free T₄ (and/or increased T₃)
• positive for TSI
• increased radioactive iodine (I-131) uptake
• homogeneous uptake on thyroid scan (only do this test in the presence of nodule)

Treatment
• thionamides
  - propylthiouracil (PTU) or methimazole (MMI)
  - inhibit thyroid hormone synthesis by inhibiting peroxidase-catalyzed reactions, thereby inhibiting organification of iodide, blocking the coupling of iodotyrosines
  - PTU also inhibits peripheral deiodination of T₄ to T₃
  - continue treatment until remission occurs (20-40% of patients achieve spontaneous remission at 6-18 mo of treatment)
• small goitre and recent onset are good indicators for long-term remission with medical therapy
• major side effects: hepatitis, agranulocytosis, and fever/arthritis
• minor side effects: rash
• iodinated contrast agents: sodium ipodate and iopanoic acid can inhibit conversion of T₄ to T₃ and are especially effective in combination with MMI
• MMI preferred vs. PTU due to longer duration of action (once daily for most), more rapid efficacy, and lower incidence of side effects
• MMI contraindicated in pregnancy (teratogenic), use PTU
• symptomatic treatment with β-blockers
• thyroid ablation with radioactive ¹³¹I if PTU or MMI trial does not produce disease remission
  - high incidence of hypothyroidism after ¹³¹I requiring lifelong thyroid hormone replacement
  - contraindicated in pregnancy
  - may worsen ophthalmopathy
• subtotal or total thyroidectomy (indicated rarely for large goitres, suspicious nodule for CA, if patient is intolerant to thionamides and refusing RAI ablation)
• risks include hypoparathyroidism and vocal cord palsy
• ophthalmopathy/orbitopathy
• smoking cessation is most important
• prevent drying
• high dose prednisone in severe cases
• orbital radiation, surgical decompression

Prognosis
• course involves remission and exacerbation unless gland is destroyed by radioactive iodine or surgery
• lifetime follow-up needed
• risk of relapse is 37%, 21%, 6% in thionamides, radioiodine ablation, and surgery groups, respectively

Subacute Thyroiditis (Thyrotoxic Phase)
Definition
• acute inflammatory disorder of the thyroid gland characterized by an initial thyrotoxic state followed by hypothyroidism eventually followed by euthyroidism in most cases
• two subtypes: painful and painless

Etiology and Pathophysiology
• acute inflammation of the thyroid gland characterized by giant cells and lymphocytes
• disruption of thyroid follicles by inflammatory process results in the release of stored hormone rather than excessive production of new thyroid hormone
• painful = viral (usually preceded by URTI), De Quervain’s (granulomatous thyroiditis)
• painless = postpartum, auto-immune, lymphocytic
  - occurs in 5-10% of postpartum mothers and is symptomatic in 1/3 of patients
**Clinical Features**
- two forms
  - painful (“De Quervain’s”) thyroid, ears, jaw, and occiput
  - painless (“Silent”)
- fever and malaise may be present, especially in De Quervain’s
- postpartum: thyrotoxicosis 2-3 mo postpartum with a subsequent hypothyroid phase at 4-8 mo postpartum
- may be mistakenly diagnosed as postpartum depression

**Laboratory Investigations**
- initial elevated free T₄, T₃, low TSH, RAIU markedly reduced
- marked elevation of ESR in painful variety only
- as disease progresses values consistent with hypothyroidism may appear

**Treatment**
- painful – high dose NSAIDs, prednisone may be required for severe pain, fever, or malaise
- iodinated contrast agents (e.g. iopanoic acid, ipodate) to inhibit peripheral conversion of T₄ to T₃
- β-adrenergic blockade is usually effective in reversing most of the hypermetabolic and cardiac symptoms in both subtypes
- if symptomatically hypothyroid, may treat short-term with thyroxine

**Prognosis**
- full recovery in most cases, but permanent hypothyroidism in 10% of painless thyroiditis
- postpartum: most resolve spontaneously without need for supplementation, however may recur with subsequent pregnancies

---

**Toxic Adenoma/Toxic Multinodular Goitre**

**Etiology and Pathophysiology**
- autonomous thyroid hormone production from a functioning adenoma that is hypersecreting T₃ and T₄
- may be singular (toxic adenoma) or multiple (toxic multinodular goitre [Plummer’s disease])

**Clinical Features**
- goitre with adenomatous changes
- tachycardia, heart failure, arrhythmia, weight loss, nervousness, weakness, tremor, and sweats
- seen most frequently in elderly people, often with presentation of atrial fibrillation

**Investigations**
- low TSH, high T₃ and T₄
- thyroid scan with increased uptake in nodule(s) and suppression of the remainder of the gland

**Treatment**
- initiate therapy with PTU or MMI to attain euthyroid state
- use high dose radioactive iodine (I-131) to ablate hyperfunctioning nodules
- β-blockers often necessary for symptomatic treatment prior to definitive therapy
- surgical excision may also be used as 1st line treatment

---

**Thyrotoxic Crisis/Thyroid Storm**

**Definition**
- acute exacerbation of all of the symptoms of thyrotoxicosis presenting in a life-threatening state secondary to uncontrolled hyperthyroidism – medical emergency!
- rare, but serious with mortality rate between 10-30%

**Etiology and Pathophysiology**
- often precipitated by infection, trauma, or surgery in a hyperthyroid patient

**Differential Diagnosis**
- sepsis, pheochromocytoma, malignant hyperthermia, drug overdose, neuroleptic malignant syndrome

**Clinical Features**
- hyperthyroidism
- extreme hyperthermia (≥40°C), tachycardia, vomiting, diarrhea, vascular collapse, hepatic failure with jaundice, and confusion
- tachyarrhythmia, CHF, shock
- mental status changes ranging from delirium to coma
Laboratory Investigations
- increased free T₃ and T₄, undetectable TSH
- ± anemia, leukocytosis, hyperglycemia, hypercalcemia, elevated LFTs

General Measures
- fluids, electrolytes, and vasopressor agents should be used as indicated
- a cooling blanket and acetaminophen can be used to treat the pyrexia
- propranolol or similar agents for β-adrenergic blockade is used, which additionally causes decreased peripheral conversion of T₄ to T₃
- use with caution in CHF patients as it may worsen condition

Specific Measures
- PTU is the anti-thyroid drug of choice and is used in high doses
- Give iodide, which acutely inhibits the release of thyroid hormone, one hour after the first dose of PTU is given
  - Sodium iodide 1 g IV drip over 12h q12h
  - Lugol’s solution 2-3 drops q8h
  - Potassium iodide (SSKI) 5 drops q8h
- dexamethasone 2-4 mg IV q6h for the first 24-48 hours lowers body temperature and inhibits peripheral conversion of T₄ to T₃

Prognosis
- probably <20% mortality rate if rapidly recognized and treated

Hypothyroidism

Definition
- clinical syndrome caused by cellular responses to insufficient thyroid hormone production

Epidemiology
- 2-3% of general population
- F:M = 10:1
- 10-20% of women over age 50 have subclinical hypothyroidism (normal T₄, TSH mildly elevated)
- iodine deficiency most common cause worldwide, but not in North America

Etiology and Pathophysiology
- primary hypothyroidism (90%)
  - inadequate thyroid hormone production secondary to intrinsic thyroid defect
  - iatrogenic: post-ablative (¹³¹I or surgical thyroidectomy)
  - autoimmune: Hashimoto’s thyroiditis, chronic thyroiditis, idiopathic, burnt out Graves’
  - hypothyroid phase of subacute thyroiditis
  - drugs: goitrogens (iodine), PTU, MMI, lithium
  - infiltrative disease (progressive systemic sclerosis, amyloid)
  - iodine deficiency
  - congenital (1/4,000 births)
  - neoplasia
- secondary hypothyroidism: pituitary hypothyroidism
  - insufficiency of pituitary TSH
- tertiary hypothyroidism: hypothalamic hypothyroidism
  - decreased TRH from hypothalamus (rare)
- peripheral tissue resistance to thyroid hormone (Refetoff syndrome)

Table 19. Interpretation of Serum TSH and Free T₄ in Hypothyroidism

<table>
<thead>
<tr>
<th>Serum TSH</th>
<th>Free T₄</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overt Primary Hypothyroidism</td>
<td>Increased</td>
</tr>
<tr>
<td>Subclinical Primary Hypothyroidism</td>
<td>Increased</td>
</tr>
<tr>
<td>Secondary Hypothyroidism</td>
<td>Decreased or not appropriately elevated</td>
</tr>
</tbody>
</table>

![Thyroid Hormone Replacement for Subclinical Hypothyroidism](Cochrane DB Syst Rev 2007;3:CD003419)

**Purpose:** To assess the effects of thyroid hormone replacement for subclinical hypothyroidism.

**Study Selection:** RCTs comparing thyroid hormone replacement with placebo in adults with subclinical hypothyroidism. Minimum duration of follow-up was one month.

**Results:** No trial assessed cardiovascular mortality or morbidity. Seven studies evaluated symptoms, mood, and quality of life with no statistically significant improvement. One study showed a statistically significant improvement in cognitive function. Six studies assessed serum lipids, there was a trend for reduction in some parameters following levothyroxine replacement. Some echocardiographic parameters improved after levothyroxine replacement therapy, like myocardial relaxation. Only four studies reported adverse events with no statistically significant differences between groups.

**Conclusions:** In current RCTs, levothyroxine replacement therapy for subclinical hypothyroidism did not result in improved survival or decreased cardiovascular morbidity. Data on health-related quality of life and symptoms did not demonstrate significant differences between intervention groups. Some evidence indicates that levothyroxine replacement improves some parameters of lipid profiles and left ventricular function.
Clinical Features

Table 20. Clinical Features of Hypothyroidism

<table>
<thead>
<tr>
<th>General</th>
<th>Fatigue, cold intolerance, slowing of mental and physical performance, hoarseness, macroglossia</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVS</td>
<td>Pericardial effusion, bradycardia, hypotension, worsening CHF + angina, hypercholesterolemia,</td>
</tr>
<tr>
<td></td>
<td>hyperhomocysteinemia, myxedema heart</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Decreased exercise capacity, hypventilation secondary to weak muscles, decreased pulmonary</td>
</tr>
<tr>
<td></td>
<td>responses to hypoxia, sleep apnea due to macroGLOSSIA</td>
</tr>
<tr>
<td>GI</td>
<td>Weight gain despite poor appetite, constipation</td>
</tr>
<tr>
<td>Neurology</td>
<td>Paresthesia, slow speech, muscle cramps, delay in relaxation phase of deep tendon reflexes</td>
</tr>
<tr>
<td></td>
<td>(&quot;hung reflexes&quot;), carpal tunnel syndrome, asymptomatic increase in CK, seizures</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Puffiness of face, periocular edema, cool and pale, dry and rough skin, dry and coarse, eyebrows</td>
</tr>
<tr>
<td></td>
<td>thinned (lateral 1/3), discolouration (carotenemia)</td>
</tr>
<tr>
<td>Hematology</td>
<td>Anemia: 10% pernicious due to presence of anti-parietal cell antibodies with Hashimoto's thyroiditis</td>
</tr>
</tbody>
</table>

Treatment

- L-thyroxine (dose range: 0.05–0.2 mg PO OD ~1.6 µg/kg/d)
- elderly patients and those with CAD: start at 0.025 mg daily and increase gradually every 6 wk (start low, go slow)
- after initiating L-thyroxine, TSH needs to be evaluated in 6 wk; dose is adjusted until TSH returns to normal reference range
- once maintenance dose achieved, follow-up TSH with patient annually
- secondary/tertiary hypothyroidism
  - monitor via measurement of free T₄ (TSH is unreliable in this setting)

CONGENITAL HYPOTHYROIDISM

- see Pediatrics, P29

Hashimoto’s Thyroiditis

- most common form of primary hypothyroidism in North America
- chronic autoimmune thyroiditis characterized by both cellular and humoral factors in the destruction of thyroid tissue
- two major forms: goitrous and atrophic; both forms share same pathophysiology but differ in the extent of lymphocytic infiltration, fibrosis, and thyroid follicular cell hyperplasia
- goitrous variant usually presents with a rubbery goitre and euthyroidism, then hypothyroidism becomes evident
  - associated with fibrosis
- atrophic variant patients are hypothyroid from the start
  - associated with thyroid lymphoma

Etiology and Pathophysiology

- defect in clone of T-suppressors leads to cell-mediated destruction of thyroid follicles
- B lymphocytes produce antibodies against thyroid components including thyroglobulin, thyroid peroxidase, TSH receptor, Na⁺/I⁻ symporter

Risk Factors

- female gender
- genetic susceptibility: increased frequency in patients with Down’s syndrome, Turner’s syndrome, certain HLA alleles, cytotoxic T-lymphocyte-associated protein 4 (CTLA-4)
- family Hx or personal Hx of other autoimmune diseases
- cigarette smoking
- high iodine intake
- stress and infection

Investigations

- high TSH, low T₄ (not necessary to measure T₃, as it will be low as well)
- presence of anti-thyroid peroxidase (TPOAb) and anti-thyroglobulin antibodies (TgAb) in serum

Treatment

- if hypothyroid, replace with L-thyroxine (analog of T₄)
Myxedema Coma

Definition
- severe hypothyroidism complicated by trauma, sepsis, cold exposure, MI, inadvertent administration of hypnotics or narcotics, and other stressful events – medical emergency!
- rare, high level of mortality when it occurs (up to 40%, despite therapy)

Clinical Features
- hallmark symptoms of decreased mental status and hypothermia; hyponatremia, hypotension, hypoglycemia, bradycardia, hypoventilation, and generalized edema often present

Investigations
- decreased T₄, increased TSH, decreased glucose
- check ACTH and cortisol for evidence of adrenal insufficiency

Treatment
- aggressive treatment required
- ABCs: ICU admission
- corticosteroids (for risk of concomitant adrenal insufficiency): hydrocortisone 100 mg q8h
- L-thyroxine 0.2-0.5 mg IV loading dose, then 0.1 mg IV OD until oral therapy tolerated; also consider T₃ therapy
- supportive measures: mechanical ventilation, vasopressor drugs, passive rewarming, IV dextrose, fluids if necessary (risk of overload)
- monitor for arrhythmia

Sick Euthyroid Syndrome

Definition
- changes in circulating thyroid hormones amongst patients with serious illness, trauma, or stress
- not due to intrinsic thyroid or pituitary disease
- initially low free T₃ may be followed by low TSH and if severe illness low free T₄
- with recovery of illness, TSH may overshoot and become transiently high

Pathophysiology
- abnormalities include alterations in
  - peripheral transport and metabolism of thyroid hormone
  - regulation of TSH secretion
  - thyroid function itself
  - may be protective during illness by reducing tissue catabolism

Labs
- initially decreased free T₃ followed by decreased TSH and finally decreased free T₄

Treatment
- treat the underlying disease; thyroid hormone replacement worsens outcomes
- thyroid function tests normalize once patient is well (initially with a transient increase in TSH)

Non-Toxic Goitre

Definition
- generalized enlargement of the thyroid gland in a euthyroid individual that does not result from inflammatory or neoplastic processes

Pathophysiology
- the appearance of a goitre is more likely during adolescence, pregnancy, and lactation because of increased thyroid hormone requirements
  - early stages: goitre is usually diffuse
  - later stages: multinodular non-toxic goitre with nodule, cyst formation and areas of ischemia, hemorrhage, and fibrosis

Etiology
- iodine deficiency or excess
- goitrogens: brassica vegetables (e.g. turnip, cassava)
- drugs: iodine, lithium, para-aminosalicylic acid
- any disorder of hormone synthesis with compensatory growth
- peripheral resistance to thyroid hormone
Treatment
• remove goitrogens
• radiiodine therapy (need very high doses, low iodine uptake, used as last resort)
• suppression with L-thyroxine (rarely done)
• surgery may be necessary for severe compressive symptoms

Complications
• compression of neck structures causing stridor, dysphagia, pain, and hoarseness
• multinodular goitre may become autonomous leading to toxic multinodular goitre and hyperthyroidism

Thyroid Nodules

Definition
• clearly defined discrete mass, separated from the thyroid parenchyma
• palpable nodules are found in approximately 5% of women and 1% of men

Etiology
• benign tumours (e.g. colloid nodule, follicular adenoma)
• thyroid malignancy
• hyperplastic area in a multinodular goitre
• cyst: true thyroid cyst, area of cystic degeneration in a multinodular goitre

Investigations

Figure 9. Approach to the evaluation of a thyroid nodule
Adapted from Dr. J Goguen, University of Toronto, MMMD 2013

Thyroid Malignancies

• see Otolaryngology, OT38

Adrenal Cortex

Adrenocorticotropic Hormone

• a polypeptide (cleaved from prohormone POMC), secreted in a pulsatile fashion from the anterior pituitary with diurnal variability (peak: 0200-0400; trough: 1800-2400)
• secretion regulated by corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP)
• stimulates growth of adrenal cortex and release of glucocorticoids, androgens and, to a limited extent, mineralocorticoids
• some melanocyte stimulating activity

Adrenocortical Hormones

Aldosterone
• a mineralocorticoid which regulates extracellular fluid (ECF) volume through Na⁺ (and Cl⁻) retention and K⁺ (and H⁺) excretion (stimulates distal tubule Na⁺/K⁺ ATPase)
• regulated by the renin-angiotensin-aldosterone system (Figure 12)
• negative feedback to juxtaglomerular apparatus (JGA) by long loop (aldosterone → volume expansion) and short loop (angiotensin II → peripheral vasoconstriction)
Figure 11. Pathways of major steroid synthesis in the adrenal gland and their enzymes

Cortisol
- a glucocorticoid, regulated by the HPA axis
- involved in regulation of metabolism; counteracts the effects of insulin
- support blood pressure, vasomotor tone
- also involved in regulation of behaviour and immunosuppression

Table 21. Physiological Effects of Glucocorticoids

<table>
<thead>
<tr>
<th>Stimulatory Effects</th>
<th>Inhibitory Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulate hepatic glucose production (gluconeogenesis)</td>
<td>Inhibit bone formation; stimulate bone resorption</td>
</tr>
<tr>
<td>Increase insulin resistance in peripheral tissues</td>
<td>Inhibit fibroblasts, causing collagen and connective tissue loss</td>
</tr>
<tr>
<td>Increase protein catabolism</td>
<td>Suppress inflammation; impair cell-mediated immunity</td>
</tr>
<tr>
<td>Stimulate leukocytosis and lymphopenia</td>
<td>inhibit growth hormone axis</td>
</tr>
<tr>
<td>Increase cardiac output, vascular tone, Na⁺ retention</td>
<td>inhibit reproductive axis</td>
</tr>
<tr>
<td>Increase PTH release, urine calcium excretion</td>
<td>inhibit vitamin D₃ and inhibit calcium uptake</td>
</tr>
</tbody>
</table>

Androgens
- sex steroids regulated by ACTH; primarily responsible for adrenarche (growth of axillary and pubic hair)
- principal adrenal androgens are dihydroepiandrosterone (DHEA), androstenedione, and 11-hydroxyandrostenedione
- proportion of total androgens (adrenal to gonadal) increases in old age
Adrenocortical Functional Workup

STIMULATION TEST
- purpose: diagnosis of hormone deficiencies
- method: measure target hormone after stimulation with tropic (pituitary) hormone

1. Tests of Glucocorticoid Reserve
- Cosyntropin (ACTH analogue) Stimulation Test
  - give 1 µg or 250 µg cosyntropin IV, then measure plasma cortisol levels at time 0, 30, and 60 min
  - physiologic response: stimulated plasma cortisol of >500 nmol/L
  - inappropriate response: inability to stimulate increased plasma cortisol
- insulin tolerance is the gold standard test used to diagnose adrenal insufficiency (see Pituitary Gland, E16)

SUPPRESSION TESTS
- purpose: diagnosis of hormone hypersecretion
- method: measure target hormone after suppression of its tropic (pituitary) hormone

1. Tests of Pituitary-Adrenal Suppressibility
- Dexamethasone (DXM) Suppression Test
  - principle: DXM suppresses pituitary ACTH → plasma cortisol should be lowered if HPA axis is normal
  - Screening Test: Overnight DXM Suppression Test
    - oral administration of 1 mg DXM at midnight → measure plasma cortisol levels the following day at 8 am
    - physiologic response: plasma cortisol <50 nmol/L, with 50-140 nmol/L being a “grey zone” (cannot be certain if normal or not)
    - inappropriate response: failure to suppress plasma cortisol
  - <20% false positive results due to obesity, depression, alcohol, other medications
  - Confirmatory Test: Other testing is used to confirm the diagnosis, such as:
    - 24 h urine free cortisol (shows overproduction of cortisol)
    - midnight salivary cortisol (if available), shows lack of diurnal variation
    - inappropriate response: remains high (normally will be low at midnight)

2. Tests of Mineralocorticoid Suppressibility
- principle: expansion of extracellular fluid volume (ECFV) → plasma aldosterone should be lowered if HPA axis were normal
- ECFV Expansion with Normal Saline (NS)
  - IV infusion of 500 mL/h of NS for 4 h → then measure plasma aldosterone levels
  - plasma aldosterone >277 pmol/L is consistent with primary hyperaldosteronism, <140 pmol/L is normal
  - inappropriate response: failure to suppress plasma aldosterone
Mineralocorticoid Excess Syndromes

**Definition**
- primary hyperaldosteronism (PH): excess aldosterone production (intra-adrenal cause)
- secondary hyperaldosteronism (SH): aldosterone production in response to excess RAAS (extra-adrenal cause)

**Etiology**
- primary hyperaldosteronism
  - aldosterone-producing adrenal adenoma (Conn's syndrome)
  - bilateral or idiopathic adrenal hyperplasia
  - glucocorticoid-remediable aldosteronism
  - aldosterone-producing adrenocortical carcinoma
  - unilateral adrenal hyperplasia
- secondary hyperaldosteronism

**Clinical Features**
- HTN
- hypokalemia (may have mild hyponatremia), metabolic alkalosis
- normal K⁺, low Na⁺ in SH (low effective circulating volume leads to ↑ ADH release) → edema
- increased cardiovascular risk: LV hypertrophy, atrial fibrillation, stroke, MI
- fatigue, weakness, paresthesia, headache; severe cases with tetany, intermittent paralysis

**Diagnosis**
- investigate plasma aldosterone to renin ratio in patients with HTN and hypokalemia
- confirmatory testing for PH: aldosterone suppression test (demonstrate inappropriate aldosterone secretion with ECFV expansion)
- imaging: CT adrenal glands

**Table 22. Diagnostic Tests in Hyperaldosteronism**

<table>
<thead>
<tr>
<th>Test</th>
<th>Primary Hyperaldosteronism</th>
<th>Secondary Hyperaldosteronism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma aldosterone to renin ratio (PAC/PRA)</td>
<td>Elevated (↑ ald, ↓ renin)</td>
<td>Normal (↑ ald, ↑ renin)</td>
</tr>
<tr>
<td>Salt loading test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A) Oral test</td>
<td>↑ urine aldosterone</td>
<td>Not performed if normal PAC/PRA</td>
</tr>
<tr>
<td>B) IV saline test</td>
<td>↑ plasma aldosterone</td>
<td></td>
</tr>
</tbody>
</table>

**Treatment**
- inhibit action of aldosterone: spironolactone, eplerenone, triamterene, amiloride (act on sodium channels)
- surgical excision of adrenal adenoma
- secondary hyperaldosteronism: treat underlying cause
**Cushing’s Syndrome**

**Definition**
- results from chronic glucocorticoid excess (endogenous or exogenous sources)

**Etiology**
- ACTH-dependent (85%) – bilateral adrenal hyperplasia and hypersecretion due to:
  - ACTH-secreting pituitary adenoma (Cushing’s disease; 80% of ACTH-dependent)
  - ectopic ACTH-secreting tumour (e.g. small cell lung carcinoma, bronchial, carcinoid, pancreatic islet cell, pheochromocytoma, or medullary thyroid tumours)
- ACTH-independent (15%)
  - long-term use of exogenous glucocorticoids
  - primary adrenocortical tumours: adenoma and carcinoma (uncommon)
  - bilateral adrenal nodular hyperplasia

**Clinical Features**
- symptoms: weakness, insomnia, mood disorders, impaired cognition, easy bruising, oligo-/amenorrhea, hirsutism, and acne (ACTH dependent)
- signs: central obesity, round face, supraclavicular and dorsal fat pads, facial plethora, proximal muscle wasting, purple abdominal striae, skin atrophy, acanthosis nigricans, HTN, hyperglycemia, osteoporosis, pathologic fractures, hyperpigmentation, hyperandrogenism if ACTH-dependent

**Diagnosis**
- complete a drug history to exclude iatrogenic Cushing’s
- perform one of: 1. 24 h urine free cortisol, 2. dexamethasone suppression test, or 3. late night salivary cortisol
- consider reasons for a false positive (e.g. pregnancy, depression, alcoholism, morbid obesity, poorly controlled DM)
- confirm with one of the remaining tests if necessary (do not rely on random cortisol, insulin tolerance, loperamide, or urinary 17-ketosteroid tests)

**Treatment**
- adrenal
  - adenoma: unilateral adrenalectomy (curative) with glucocorticoid supplementation post-operatively
  - carcinoma: adjunctive chemotherapy often not useful (frequent metastases, poor prognosis)
  - medical treatment: mitotane, ketoconazole to reduce cortisol
- pituitary
  - trans-sphenoidal resection, with glucocorticoid supplement post-operatively
- ectopic ACTH tumour (paraneoplastic syndrome): usually bronchogenic cancer (poor prognosis)
  - surgical resection, if possible; chemotherapy/radiation for primary tumour
  - agents blocking adrenal steroid synthesis: metyrapone or ketoconazole

**Congenital Adrenal Hyperplasia**
- see Pediatrics, P30

**Hyperandrogenism**

**Definition**
- state of having excessive secretion of androgens (DHEA, DHEA sulfate, testosterone)

**Etiology and Pathophysiology**

<table>
<thead>
<tr>
<th>Table 23. Etiology of Hyperandrogenism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Constitutional/Familial</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Medications</strong></td>
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<tr>
<td><strong>Ovarian</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Adrenal</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Pituitary</strong></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>
Clinical Features
Females
- hirsutism
  - male pattern growth of androgen-dependent terminal body hair in women: back, chest, upper abdomen, face, linea alba
  - Ferriman-Gallwey scoring system is used to quantify severity of hirsutism
- virilization
  - masculinization: hirsutism, temporal balding, clitoral enlargement, deepening of voice, acne
  - increase in musculature
- defeminization
  - loss of female secondary sex characteristics (i.e. amenorrhea, ↓ breast size, infertility)

Males
- minimal effects on hair, muscle mass, etc.
- inhibition of gonadotropin secretion may cause reduction in: testicular size, testicular testosterone production, and spermatogenesis

Investigations
- testosterone, DHEA-S as a measure of adrenal androgen production
- LH/FSH (commonly in PCOS >2.5)
- 17-OH progesterone, elevated in CAH due to 21-OH deficiency; check on day 3 of menstrual cycle with a progesterone level
- for virilization: CT/MRI of adrenals and ovaries (identify tumours)
- if PCOS, check blood glucose, lipids, 75 g OGTT

Treatment
- discontinue causative medications
- antiandrogens, e.g. spironolactone
- oral contraceptives (increase SHBG, which binds androgens>estrogens; reduce ovarian production of androgens)
- surgical resection of tumour
- low dose glucocorticoid ± mineralocorticoid if CAH suspected
- treat specific causative disorders, e.g. tumours, Cushing’s, etc.
- cosmetic therapy (laser, electrolysis)

Adrenocortical Insufficiency

Definition
- a state of inadequate cortisol and/or aldosterone production by the adrenal glands

Etiology

PRIMARY (ADDISON’S DISEASE)

<table>
<thead>
<tr>
<th>Table 24. Etiology of Primary Adrenocortical Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Autoimmune (70-90%)</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
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<td></td>
</tr>
<tr>
<td><strong>Infiltrative</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Drugs</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
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<tr>
<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>
SECONDARY ADRENOCORTICAL INSUFFICIENCY

- inadequate pituitary ACTH secretion
- multiple etiologies (see Hypopituitarism, E20), including withdrawal of exogenous steroids

Clinical Features

### Table 25. Clinical Features of Primary and Secondary Adrenal Insufficiency (AI)

<table>
<thead>
<tr>
<th></th>
<th>Primary AI (Addison’s or Acute AI)</th>
<th>Secondary AI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and Mucosa</td>
<td>Dark (palmar crease, extensor surface)</td>
<td>Pale</td>
</tr>
<tr>
<td>Potassium</td>
<td>High</td>
<td>Normal</td>
</tr>
<tr>
<td>Sodium</td>
<td>Low</td>
<td>Normal or Low</td>
</tr>
<tr>
<td>Metabolic Acidosis</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Associated Diseases</td>
<td>Primary hypothyroidism, type 1 DM, vitiligo, neurological deficits</td>
<td>Central hypogonadism or hypothyroidism, growth hormone deficiency, DI, headaches, visual abnormalities</td>
</tr>
<tr>
<td>Associated Symptoms</td>
<td>Weakness, fatigue, weight loss, hypotension, salt craving, postural dizziness, myalgia, arthralgia Gl: N/V, abdominal pain, diarrhea</td>
<td>Same except: NO salt craving Gl less common</td>
</tr>
<tr>
<td>Diagnostic Test</td>
<td>Insulin tolerance test Cosyntropin Stimulation Test High morning plasma ACTH</td>
<td>Insulin tolerance test Cosyntropin Stimulation Test Low morning plasma ACTH</td>
</tr>
</tbody>
</table>

Adapted from: Salvatori R. JAMA 2005;294:2481-2488

Treatment

- acute condition – can be life-threatening
  - IV NS in large volumes (2-3 L); add D5W if hypoglycemic from adrenal insufficiency
  - hydrocortisone 50-100 mg IV q6-8h for 24h, then gradual tapering
  - identify and correct precipitating factors
- maintenance
  - hydrocortisone 15-20 mg total daily dose, in 2-3 divided doses, highest dose in the AM
  - Florinef® (fludrocortisone, synthetic mineralocorticoid) 0.05-0.2 mg PO daily if mineralocorticoid deficient increase dose of steroids 2-3 fold for a few days during moderate-severe illness (e.g. with vomiting, fever)
  - major stress (e.g. surgery, trauma) requires 150-300 hydrocortisone IV daily divided into 3 doses
  - medical alert bracelet and instructions for emergency hydrocortisone/dexamethasone IM/SC injection

Adrenal Medulla

Catecholamine Metabolism

- catecholamines are synthesized from tyrosine in postganglionic sympathetic nerves (norepinephrine) and chromaffin cells of adrenal medulla (epinephrine)
- broken down into metanephrines and other metabolites (VMA, HVA) and excreted in urine

Pheochromocytoma

Definition

- rare catecholamine secreting tumour derived from chromaffin cells of the sympathetic system

Epidemiology

- most commonly a single tumour of adrenal medulla
- rare cause of HTN (<0.2% of all hypertensives)

Etiology and Pathophysiology

- most cases sporadic (80%)
- familial: associated with multiple endocrine neoplasia II (MEN IIA and IIB) (50% penetrance; i.e. 50% of people with the mutation get pheochromocytoma), von Hippel-Lindau (10-20% penetrance), paraganglioma (20% penetrance), or neurofibromatosis type 1 (0.1-5.7% penetrance)
- tumours, via unknown mechanism, able to synthesize and release excessive catecholamines
Clinical Features
• 50% suffer from paroxysmal HTN; the rest have sustained HTN
• classic triad (not found in most patients): episodic "pounding" headache, palpitations/tachycardia, diaphoresis
• other symptoms: tremor, anxiety, chest or abdominal pain, N/V, visual blurring, weight loss, polyuria, polydipsia
• other signs: orthostatic hypotension, papilledema, hyperglycemia, dilated cardiomyopathy
• symptoms may be triggered by stress, exertion, anesthesia, abdominal pressure, certain foods (especially tyramine containing foods)

Investigations
• urine catecholamines
  ▪ increased catecholamine metabolites (metanephrines) and free catecholamines
  ▪ plasma metanephrines if available (most sensitive)
  ▪ cut-off values will depend on assay used
• CT abdomen
  ▪ if negative, whole body CT and meta-iodo-benzoguanidine (MIBG) scintigraphy, Octreoscan, or MRI

Treatment
• surgical removal of tumour (curative) with careful pre- and post-operative ICU monitoring
• adequate pre-operative preparation
  ▪ α-blockade for BP control: doxazosin or calcium channel blockers (10-21 d pre-operative), IV phentolamine (perioperative, if required)
  ▪ β-blockade for HR control once α blocked for a few days
  ▪ metyrosine (catecholamine synthesis inhibitor) + phenoxybenzamine or prazosin
  ▪ volume restoration with vigorous salt-loading and fluids
• rescreen urine 1-3 mo post-operatively
• screen urine in first degree relatives; genetic testing in patients <50 yr old

Disorders of Multiple Endocrine Glands

Multiple Endocrine Neoplasm

• neoplastic syndromes involving multiple endocrine glands
• tumours of neuroectodermal origin
• autosomal dominant inheritance with variable penetrance
• genetic screening for RET proto-oncogene on chromosome 10 has long-term benefit in MEN II
  ▪ early cure and prevention of medullary thyroid cancer

Table 26. MEN Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissues Involved</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEN I (chromosome 11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wermer’s Syndrome</td>
<td>Pituitary (15-42%)</td>
<td>Headache, visual field defects, often non-secreting but may secrete GH (acromegaly) and PRL (galactorrhea, erectile dysfunction, decreased libido, amenorrhea)</td>
</tr>
<tr>
<td></td>
<td>Anterior pituitary adenoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Parathyroid (≥95%)</td>
<td>Nephrolithiasis, bone abnormalities, MSK complaints, symptoms of hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Primary hyperparathyroidism from hyperplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Entero-pancreatic endocrine (30-80%)</td>
<td>Hypoglycemia</td>
</tr>
<tr>
<td></td>
<td>Pancreatic islet cell tumours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gastrinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Insulinomas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vasoactive intestinal peptide (VIP)-omas</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Glucagonoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carcinoid syndrome</td>
<td></td>
</tr>
<tr>
<td>MEN II (chromosome 10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Ila Sipple’s Syndrome</td>
<td>Thyroid (&gt;90%)</td>
<td>Physical signs are variable and often subtle</td>
</tr>
<tr>
<td></td>
<td>Medullary thyroid cancer (MTC)</td>
<td>Neck mass or thyroid nodule; non-tender, anterior lymph nodes</td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla (40-50%)</td>
<td>HTN, palpitations, headache, sweating</td>
</tr>
<tr>
<td></td>
<td>Pheochromocytoma (40-50%)</td>
<td>Symptoms of hypercalcemia</td>
</tr>
<tr>
<td></td>
<td>Parathyroid (10-20%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st parathyroid hyperplasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin</td>
<td>Scaly skin rash</td>
</tr>
<tr>
<td></td>
<td>Cutaneous lichen amyloidosis</td>
<td></td>
</tr>
</tbody>
</table>

MEN I – Wermer’s Syndrome Affects the 3 Ps
Pituitary
Parathyroid
Pancreas
Table 26. MEN Classification (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Tissues Involved</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>2. Familial Medullary</td>
<td>Thyroid</td>
<td>MTC without other clinical manifestations of MEN IIa or IIb</td>
</tr>
<tr>
<td>Thyroid Ca</td>
<td>MTC (≥95%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>MTC: most common component, more aggressive and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>earlier onset than MEN IIa, HTN, palpitations, headache, sweating</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chronic constipation; megacolon</td>
</tr>
<tr>
<td>3. IIb</td>
<td>Thyroid</td>
<td>Marfanoid habitus (no aortic abnormalities)</td>
</tr>
<tr>
<td></td>
<td>MTC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adrenal medulla</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phaeochromocytoma (≥50%)</td>
<td></td>
</tr>
<tr>
<td>Neurons</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mucosal neuroma, intestinal</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ganglioneuromas (100%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MSK (100%)</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN I</td>
<td>laboratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• may consider genetic screening for MEN-1 mutation in index patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• gastrinoma: elevated serum gastrin level (&gt;200 ng/mL) after IV injection of secretin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• insulinoma: reduced fasting blood glucose (hypoglycemia) with elevated insulin and C-peptide levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• glucagonoma: elevated blood glucose and glucagon levels</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• pituitary tumours: assess GH, IGF-1, and prolactin levels (for over-production), TSH, free T4, 8 AM cortisol, LH, FSH, bioavailable testosterone or estradiol (for underproduction due to mass effect of tumour)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• hyperparathyroidism: serum Ca$^{2+}$ and albumin, PTH levels; bone density scan (DEXA)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>imaging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• MRI for pituitary tumours, gastrinoma, insulinoma</td>
<td></td>
</tr>
<tr>
<td>MEN II</td>
<td>laboratory</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• genetic screening for RET mutations in all index patients</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• pentagastrin ± calcium stimulation test if calcitonin level is within reference range</td>
<td></td>
</tr>
<tr>
<td></td>
<td>imaging</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• CT or MRI of adrenal glands, metaiodobenzylguanidine (MIBG) scan for phaeochromocytoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• octreoscan and/or radionuclide scanning for determining the extent of metastasis</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MEN I</td>
<td>medical</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• proton pump inhibitor (PPI) for acid hypersecretion in gastrinoma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• cabergoline or other dopamine agonists to suppress prolactin secretion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• somatostatin for symptomatic carcinoid tumours</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• surgery for hyperparathyroidism, insulinoma, glucagonoma, pituitary tumours (if medical treatment fails for the latter)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• trans-sphenoidal approach with prn external radiation</td>
<td></td>
</tr>
<tr>
<td>MEN II</td>
<td>surgery for MEN IIa with pre-operative medical therapy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• prostaglandin inhibitors to alleviate diarrhea associated with thyroid cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• α-blocker for at least 10-21 d for phaeochromocytoma pre-operatively</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• hydration, calcitonin, IV bisphosphonates for hypercalcemia</td>
<td></td>
</tr>
</tbody>
</table>

Calcium Homeostasis

- normal total serum Ca$^{2+}$: 2.2-2.6 mmol/L
- ionic/free Ca$^{2+}$ levels: 1.15-1.31 mmol/L
- serum Ca$^{2+}$ is about 40% protein bound (mostly albumin), 50% ionized, and 10% complexed with PO43- and citrate
- regulated mainly by two factors: parathyroid hormone (PTH) and vitamin D
- actions mainly on three organs: GI tract, bone, and kidney
Table 27. Major Regulators in Calcium Homeostasis

<table>
<thead>
<tr>
<th>Major Regulators</th>
<th>Source</th>
<th>Regulation</th>
<th>Net Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTH</td>
<td>Parathyroid glands</td>
<td>Stimulated by low serum Ca(^{2+}) and high serum PO(_{4}^{3-}); inhibited by chronic low serum Mg(^{2+}), high serum Ca(^{2+}), and calcitriol</td>
<td>↑ Ca(^{2+}); ↓ Calcitriol</td>
</tr>
<tr>
<td>Calcitriol ((1,25-(OH)<em>{2}D</em>{3}))</td>
<td>Dietary intake, synthesized from cholesterol</td>
<td>Renal calcitriol production is stimulated by low serum PO(<em>{4}^{3-}) and PTH; inhibited by high serum PO(</em>{4}^{3-}) and calcitriol in negative feedback</td>
<td>↑ Ca(^{2+}); ↑ PO(_{4}^{3-})</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>Thyroid C cells</td>
<td>Stimulated by pentagastrin (GI hormone) and high serum Ca(^{2+}); inhibited by low serum Ca(^{2+}) (in pharmacologic doses)</td>
<td>↓ Ca(^{2+}); ↓ PO(_{4}^{3-})</td>
</tr>
<tr>
<td>Mg(^{2+})</td>
<td>Major intracellular divalent cation</td>
<td>See section on Magnesium</td>
<td>Cofactor for PTH secretion</td>
</tr>
<tr>
<td>PO(_{4}^{3-})</td>
<td>Intracellular anion found in all tissues</td>
<td>See section on Phosphate</td>
<td>↓ Ca(^{2+})</td>
</tr>
</tbody>
</table>

Figure 15. Parathyroid hormone (PTH) regulation

**Hypercalcemia**

**Definition**
- total corrected serum Ca\(^{2+}\) >2.6 mmol/L OR ionized Ca\(^{2+}\) >1.35 mmol/L
- hypercalcemia often diagnosed incidentally

**Approach to Hypercalcemia**
1. Is the patient hypercalcemic? (correct for albumin – see sidebar)
2. Is the PTH high/normal or low?
3. If PTH is low, is phosphate high/normal or low? If phosphate is high/normal is the level of vitamin D metabolites high or low?
**Clinical Features**
- symptoms depend on the absolute Ca²⁺ value and the rate of its rise (may be asymptomatic)

**Table 28. Symptoms of Hypercalcemia**

<table>
<thead>
<tr>
<th>Cardiovascular</th>
<th>GI</th>
<th>Renal</th>
<th>Rheumatological</th>
<th>MSK</th>
<th>Psychiatric</th>
<th>Neurologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>HTN</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anhydrosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short QT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deposition of Ca²⁺ on valves, coronary arteries, myocardial fibres</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td></td>
<td>Polyuria (Nephrogenic DI)</td>
<td>Gout</td>
<td>&gt;3 mmol/L (12 mg/dL)</td>
<td>Hypotonia</td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td></td>
<td>Polydipsia</td>
<td>Chondrocalcinosis</td>
<td>Increased alertness</td>
<td>Hyporeflexia</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td>Nephrolithiasis (stones)</td>
<td>Bone pain (bones)</td>
<td>Anxiety</td>
<td>Myopathy</td>
<td></td>
</tr>
<tr>
<td>Vomiting (groans)</td>
<td></td>
<td>Renal failure (irreversible)</td>
<td>&gt;5 mmol/L (16 mg/dL)</td>
<td>Depression</td>
<td>Paresis</td>
<td></td>
</tr>
<tr>
<td>PUD</td>
<td></td>
<td>Dehydration</td>
<td>&gt;4 mmol/L (16 mg/dL)</td>
<td>Organic brain syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td>Psychosis (moans)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hypercalcemic crisis (usually >4 mmol/L or 16 mg/dL):** primary symptoms include oliguria/anuria and mental status changes (including somnolence and eventually coma) → this is a medical emergency and should be treated immediately!

**Treatment**
- treatment depends on the Ca²⁺ level and the symptoms
- treat acute, symptomatic hypercalcemia aggressively
- treat the underlying cause of the hypercalcemia

**Figure 16. Differential diagnosis of hypercalcemia**

**Initial investigations:** PTH, PO₄³⁻, Mg²⁺, Urine Ca²⁺, creatinine

- Normal or ↑ PTH
  - Familiar Hypocalciuric Hypercalcemia (FHH): Ca²⁺ receptor gene defect
  - Primary Hyperparathyroidism: Solitary adenoma (81%) Carcinoma (15%) MEN I and Ila
  - Tertiary Hyperparathyroidism: Increased PTH after prolonged secondary hyperparathyroidism due to renal failure

- ↑ PTH (related to ↑ PTHrP)
  - Hypervitaminosis D: Excessive intake of Vit D or its metabolites
  - Low Vit D metabolites
  - Drugs: Lithium
  - Familial Hypocalciuric Hypercalcemia (FHH): Ca²⁺ receptor gene defect
  - Primary Hyperparathyroidism: Solitary adenoma (81%) Carcinoma (15%) MEN I and Ila
  - Tertiary Hyperparathyroidism: Increased PTH after prolonged secondary hyperparathyroidism due to renal failure

- ↓ PTH
  - Humoral mediation: Lung cancer, RCC, pheochromocytoma
  - Low Vit D metabolites
  - Drugs: theophylline, thiazide diuretics, estrogen/tamoxifen

**Corrected Ca²⁺ (mmol/L) = measured Ca²⁺ + 0.02 (40 – albumin)**

For every decrease in albumin by 10, increase in Ca²⁺ by 0.2
- Benign (less likely malignant): Ca²⁺ < 2.75 mmol/L
- Pathologic (more likely malignant): Ca²⁺ > 3.25 mmol/L

**The symptoms and signs of hypercalcemia include:**
- "Bones, stones, groans, and psychic overtones"

**The most common cause of hypercalcemia in hospital is malignancy-associated hypercalcemia**
- Usually occurs in the later stages of disease
- Most commonly seen in lung, renal, breast, ovarian, and squamous tumours, as well as lymphoma and multiple myeloma

**Mechanisms:**
- Secretion of parathyroid hormone-related protein (PTHrP) which mimics PTH action by preventing renal calcium excretion and activating osteoclast-induced bone resorption
- Cytokines in multiple myeloma
- Calcitriol production by lymphoma
- Osteolytic bone metastases direct effect
- Excess PTH in parathyroid cancer
Hypocalcemia

Definition
- total corrected serum Ca²⁺ <2.2 mmol/L.

Table 30. Clinical Features of Hypocalcemia

<table>
<thead>
<tr>
<th>Acute Hypocalcemia</th>
<th>Chronic Hypocalcemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paresthesia</td>
<td>CNS: lethargy, seizures, psychosis, basal ganglia calcification, Parkinson’s, dystonia, hermiltonism, papilledema, pseudotumour cerebri</td>
</tr>
<tr>
<td>Laryngospasm (with stridor)</td>
<td>Thymus changes: prolonged QT interval → Torsades de pointes (ventricular tachycardia)</td>
</tr>
<tr>
<td>Tetany</td>
<td>GI: steatorrhea</td>
</tr>
<tr>
<td>Chvostek’s sign (tap CN VII)</td>
<td>ENDO: impaired insulin release</td>
</tr>
<tr>
<td>Trouseau’s sign (carpal spasm)</td>
<td>SKIN: dry, scaling, alopecia, brittle and transversely fissured nails, candidiasis, abnormal dentition</td>
</tr>
<tr>
<td>ECG changes</td>
<td>OCULAR: cataracts</td>
</tr>
<tr>
<td>Delirium</td>
<td>MSK: generalized muscle weakness and wasting</td>
</tr>
<tr>
<td>Psychiatric SX: emotional instability, anxiety, and depression</td>
<td></td>
</tr>
</tbody>
</table>

Approach to Hypocalcemia
1. Is the patient hypocalcemic?
2. Is the PTH high or low?
3. If PTH is high, is phosphate low or normal?
4. Is the Mg²⁺ level low?

Approach to Treatment
- correct underlying disorder
- mild/asymptomatic (ionized Ca²⁺ >0.8 mmol/L)
  - treat by increasing dietary Ca²⁺ by 1000 mg/d
  - calcitriol 0.25 µg/d (especially in renal failure)
- acute/asymptomatic hypocalcemia (ionized Ca²⁺ <0.7 mmol/L)
  - immediate treatment required
  - IV calcium gluconate 1-2 g over 10-20 min followed by slow infusion if necessary
  - goal is to raise Ca²⁺ to low normal range (2.0-2.1 mmol/L) to prevent symptoms but allow maximum stimulation of PTH secretion
  - if PTH recovery not expected, requires long-term therapy with calcitriol and calcium
- do not correct hypocalcemia if asymptomatic and suspected to be transient

Differential Diagnosis of Hypercalcemia
• Primary hyperparathyroidism
• Malignancy: hematologic, humoral, skeletal metastases (>90% from 1 or 2)
• Renal disease: tertiary hyperparathyroidism
• Drugs: calcium carbonate, milk alkali syndrome, thiazide, lithium, theophylline, vitamin A/D intoxication
• Familial hypocalciuric hypercalcemia
• Granulomatous disease: sarcoidosis, TB, Hodgkin’s lymphoma
• Thyroid disease: thyrotoxicosis
• Adrenal disease: adrenal insufficiency, pheochromocytoma
• Immobilization

Watch Out for:
• Volume depletion via diuresis
• Arrhythmias

Acute Management of Hypercalcemia/ Hypercalcemic Crisis
• Volume expansion (e.g. NS IV 300-500 cc/h): initial therapy
• Calcitriol: transient, partial response
• Bisphosphonate: treatment of choice
• Corticosteroid: most useful in vit D toxicity, granulomatous disease, some malignancies
• Saline diuresis + loop diuretic (for volume overload): temporary measure

Hypomagnesemia can impair PTH secretion and action

Differential Diagnosis of Tetany
• Hypocalcemia
• Metabolic alkalosis (with hyperventilation)
• Hypokalemia
• Hypomagnesemia

Signs and Symptoms of Acute Hypocalcemia
• Paresthesia: perioral, hands, and feet
• Chvostek’s sign: percussion of the facial nerve just anterior to the external auditory meatus elicits ipsilateral spasm of the orbicularis oculi or orbicularis oris muscles
• Trouseau’s sign: inflation of a blood pressure cuff above systolic pressure for 3 min elicits carpal spasm and paresthesia

Transient hypoparathyroidism (resulting in hypocalcemia) common after subtotal thyroidectomy (permanent in <3% of surgeries)
Hyperphosphatemia

Definition
- serum phosphate >1.45 mmol/L
- critical role in the development of secondary hyperparathyroidism and renal osteodystrophy in patients with advanced CKD and on dialysis

Table 31. Etiology of Hyperphosphatemia

<table>
<thead>
<tr>
<th>Increased Phosphate Load</th>
<th>Reduced Renal Clearance</th>
<th>Pseudohyperphosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI intake (rectal enema, GI bleeding)</td>
<td>Acute/chronic renal failure</td>
<td>Hyperglobulinemia</td>
</tr>
<tr>
<td>IV phosphate load (K-Phos®, blood transfusion)</td>
<td>Hypoparathyroidism</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Endogenous phosphate (tumour lysis syndrome, rhabdomyolysis, hemolysis, lactic and ketoacidosis)</td>
<td>Acromegaly</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Vit D related</td>
<td>Tumour calcinosis (ability of kidney to specifically clear phosphate is defective)</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td>Low Mg²⁺</td>
<td>Secondary Hyperparathyroidism: Appropriate PT gland response to low serum Ca²⁺</td>
<td></td>
</tr>
<tr>
<td>Low Mg²⁺</td>
<td>Hereditary Vit D Resistant Rickets Type II: Receptor defect</td>
<td></td>
</tr>
<tr>
<td>Normal or ↓ PTH</td>
<td>Chronic Renal Failure Vit D Dependent Rickets Type I: Renal 1-α-hydroxylase deficiency</td>
<td></td>
</tr>
<tr>
<td>↑ PTH</td>
<td>DCalcitriol (1,25-(OH)₂ Vit D)</td>
<td></td>
</tr>
<tr>
<td>↓ PTH</td>
<td>DCalcitriol (25-OH Vit D)</td>
<td></td>
</tr>
<tr>
<td>↑ Intake and/or Malabsorption: e.g. celiac disease, IBD, gastric bypass, CF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nephrotic Syndrome: Lose Vit D binding protein</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- non-specific, include ectopic calcification, renal osteodystrophy

Treatment
- acute: hemodialysis if symptomatic
- chronic: low PO₄³⁻ diet, phosphate binders (e.g. CaCO₃ or lanthanum carbonate with meals)

Hypophosphatemia

Definition
- serum phosphate <0.85 mmol/L

Table 32. Etiology of Hypophosphatemia

<table>
<thead>
<tr>
<th>Inadequate Intake</th>
<th>Renal Losses</th>
<th>Excessive Skeletal Mineralization</th>
<th>Shift into ICF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starvation Intake Malabsorption (diarrhea, steatorrhea) Antacid use Alcoholism</td>
<td>Hyperparathyroidism</td>
<td>Hyperparathyroidism</td>
<td>Hyperparathyroidism</td>
</tr>
<tr>
<td></td>
<td>Diuretics</td>
<td>Parathyroidectomy: Post surgical correction of primary hyperparathyroidism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>X-linked or AD</td>
<td>Fanconi syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hypophosphatemic rickets</td>
<td>Multiple myeloma</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fanconi syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ PTH</td>
<td>Osteoblastic metastases</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ PTH</td>
<td>Post parathyroidectomy (referred to as ‘hungry bone syndrome’)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ PO₄³⁻</td>
<td>Recovery from metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↓ PO₄³⁻</td>
<td>Respiratory alkalosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCalcitriol (1,25-(OH)₂ Vit D)</td>
<td>Severe burns can cause hypophosphatemia due to PO₄³⁻ losses through the skin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DCalcitriol (25-OH Vit D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Calcitriol (1,25-(OH)₂ Vit D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Calcitriol (25-OH Vit D)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ Calcitriol (25-OH Vit D)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Symptoms usually present when phosphate <0.32 mmol/L (1.0 mg/dL)
Treat asymptomatic patients if phosphate <0.64 mmol/L (2.0 mg/dL)
Severe burns can cause hypophosphatemia due to PO₄³⁻ losses through the skin
Clinical Features
• non-specific (CHF, coma, hypotension, weakness, defective clotting)

Treatment
• treat underlying cause
  • Oral PO₄³⁻: 2-4 g/d divided bid-qid (start at 1 g/d to minimize diarrhea)
  • IV PO₄³⁻: only for severely symptomatic patients or inability to tolerate oral therapy

Hypermagnesemia

Definition
• serum magnesium >0.85 mmol/L

Etiology
• AKI/CRF
• Mg²⁺-containing antacids or enemas
• IV administration of large doses of MgSO₄ (e.g. for preeclampsia; see Obstetrics, OB25)

Clinical Features
• rarely symptomatic
• drowsiness, hyporeflexia, respiratory depression, heart block, cardiac arrest, hypotension

Treatment
• discontinue Mg²⁺-containing products
• IV calcium (Mg²⁺-antagonist) for acute reversal of magnesium toxicity
• dialysis if renal failure

Hypomagnesemia

Definition
• serum magnesium <0.70 mmol/L

Etiology
• GI losses
  • starvation/malabsorption
  • vomiting/diarrhea
  • alcoholism
  • acute pancreatitis
• excess renal loss
  • 2° hyperaldosteronism due to cirrhosis and CHF
  • hyperglycemia
  • hypokalemia
  • hypercalcemia
  • loop and thiazide-type diuretics
  • nephrotoxic medications
  • proton-pump inhibitors

Clinical Features
• seizures, paresis, Chvostek and Trousseau signs, ECG changes (widened QRS, prolonged PR, T-wave abnormalities), and arrhythmias including Torsades de pointes

Treatment
• treat underlying cause
• oral Mg²⁺ salts unless patients have seizures or other severe symptoms
• Mg²⁺ IM/IV; cellular uptake of Mg²⁺ is slow, therefore repletion requires sustained correction
• discontinue diuretics
  • in patients requiring diuretics, use a K⁺-sparing diuretic to minimize magnesuria

Metabolic Bone Disease

Osteoporosis

Definition
• a condition characterized by decreased bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture
• bone mineral density (BMD) ≥2.5 standard deviations below the peak bone mass for young adults (i.e. T-score ≤−2.5)
• osteopenia: BMD with T-score between -1.0 and -2.5

ETIOLOGY AND PATHOPHYSIOLOGY

Primary Osteoporosis (95% of osteoporosis in women & 80% in men)
• primary type 1: most common in post-menopausal women, due to decline in estrogen, worsens with age
• primary type 2: occurs after age 75, seen in females and males at 2:1 ratio, possibly due to zinc deficiency

Online Clinical Tools
CAROC
www.osteoporosis.ca/multimedia/pdf/CAROC.pdf
FRAX
www.shef.ac.uk/FRAX/tool.aspx
Secondary Osteoporosis
• gastrointestinal diseases
  ° gastrectomy
  ° malabsorption (e.g. celiac disease)
  ° chronic liver disease
• bone marrow disorders
  ° multiple myeloma
  ° lymphoma
  ° leukemia
• endocrinopathies
  ° Cushing’s syndrome
  ° hyperparathyroidism
  ° hyperthyroidism
  ° premature menopause
  ° DM
  ° hypogonadism
• malignancy
  ° secondary to chemotherapy
  ° myeloma

Clinical Features
• commonly asymptomatic
• height loss due to collapsed vertebrae
• fractures: most commonly in hip, vertebrae, humerus, and wrist
  ° fragility fractures: fracture with fall from standing height
  ° Dowager’s hump: collapse fracture of vertebral bodies in mid-dorsal region
  ° x-ray: vertebral compression and crush fractures, wedge fractures, “codfish” sign

Approach to Osteoporosis
1. Assess risk factors for osteoporosis on history and physical
2. Decide if patient requires BMD testing with dual-energy x-ray absorptiometry (DEXA): men
3. Initial investigations
  • all patients with osteoporosis: calcium corrected for albumin, CBC, creatinine, ALP, TSH
  • also consider serum and urine protein electrophoresis, celiac workup, and 24 h urinary Ca2+

4. Assess 10-yr fracture risk by combining BMD result and risk factors (only if ≥50 yr)
5. For all patients being assessed for osteoporosis, encourage appropriate lifestyle changes
(see Table 35)

Table 33. Indications for BMD Testing

<table>
<thead>
<tr>
<th>Older Adults (age ≥50 yr)</th>
<th>Younger Adults (age &lt;50 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All women and men age ≥65 yr</td>
<td>Fragility fracture</td>
</tr>
<tr>
<td>Menopausal women, and men aged 50-64 yr with clinical risk factors for fracture:</td>
<td></td>
</tr>
<tr>
<td>Fragility fracture after age 40</td>
<td>Prolonged use of glucocorticoids</td>
</tr>
<tr>
<td>Prolonged glucocorticoid use</td>
<td>Use of other high-risk medications (aromatase inhibitors, androgen deprivation therapy, anticonvulsants)</td>
</tr>
<tr>
<td>Other high-risk medication use (aromatase inhibitors, androgen deprivation therapy)</td>
<td>Hypogonadism or premature menopause</td>
</tr>
<tr>
<td>Parental hip fracture</td>
<td>Malabsorption syndrome</td>
</tr>
<tr>
<td>Vertebral fracture or osteopenia identified on x-ray</td>
<td>Primary hyperparathyroidism</td>
</tr>
<tr>
<td>Current smoking</td>
<td>Other disorders strongly associated with rapid bone loss and/or fracture</td>
</tr>
<tr>
<td>High alcohol intake</td>
<td>Type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (&lt;45 yr), Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. inflammatory bowel disease)</td>
</tr>
<tr>
<td>Low body weight (&lt;60 kg) or major weight loss (&gt;10% of weight at age 25 yr)</td>
<td></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>Other disorders strongly associated with osteoporosis: primary hyperparathyroidism, type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (&lt;45 yr), Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD and chronic inflammatory conditions (e.g. inflammatory bowel disease)</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Signs of Fractures or Osteoporosis
• Height loss >3 cm (Sn 92%)
• Weight <51 kg
• Kyphosis (Sp 92%)
• Tooth count <20 (Sp 92%)
• Grip strength
• Armspan-height difference >5 cm (Sp 95%)
• Wall-occiput distance >0 cm (Sp 87%)
• Rib-pelvis distance >2 finger breadth (Sn 88%)
Table 34. Osteoporosis Risk Stratification

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Fracture Risk</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>10-yr fracture risk &lt;10%</td>
<td>Unlikely to benefit from pharmacotherapy; encourage lifestyle changes</td>
</tr>
<tr>
<td></td>
<td>Reassess risk in 5 yr</td>
<td></td>
</tr>
<tr>
<td>Medium Risk</td>
<td>10-yr fracture risk 10-20%</td>
<td>Discuss patient preference for management and consider additional risk factors</td>
</tr>
<tr>
<td></td>
<td>Factors that warrant consideration for pharmacological therapy:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Additional vertebral fracture(s) identified on vertebral fracture assessment (VFA) or lateral spine x-ray</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Previous wrist fracture in individuals ≥65 or with T-score ≤-2.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Lumbar spine T-score much lower than femoral neck T-score</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rapid bone loss</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Men receiving androgen-deprivation therapy for prostate cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Women receiving aromatase-inhibitor therapy for breast cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Long-term or repeated systemic glucocorticoid use (oral or parenteral) that does not meet the conventional criteria for recent prolonged systemic glucocorticoid use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Recurrent falls (defined as falling 2 or more times in the past 12 mo)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Other disorders strongly associated with osteoporosis</td>
<td></td>
</tr>
</tbody>
</table>

Repeat BMD and reassess risk every 1-3 yr initially

Table 35. Treatment of Osteoporosis in Women and Men

### Treatment for Both Men and Women

<table>
<thead>
<tr>
<th>Lifestyle</th>
<th>Drug Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet: Elemental calcium 1000-1200 mg/d; Vit D 1000 IU/d</td>
<td>Bisphosphonate: inhibitors of osteoclast binding</td>
</tr>
<tr>
<td>Exercise: 3x30 min weight-bearing exercises/wk</td>
<td>1st line in prevention of hip, nonvertebral, and vertebral # (Grade A): alendronate, risedronate, zoledronic acid</td>
</tr>
<tr>
<td>Stop/avoid osteoporosis-inducing medications</td>
<td>2nd line (Grade B): etidronate</td>
</tr>
</tbody>
</table>

### RANKL Inhibitors

| Parathyroid Hormone | Yes fragility #: 18-24 mo duration |

| Calcitonin (2nd line) osteoclast receptor binding | YES fragility #: Calcitonin 200 IU nasally OD with Calcitriol 0.25 µg bid |

### Treatment Specific to Post-Menopausal Women

<table>
<thead>
<tr>
<th>SERM (selective estrogen-receptor modulator): agonistic effect on bone but antagonistic effect on uterus and breast</th>
<th>Raloxifene: 1st line in prevention of vertebral # (Grade A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• +ve: prevents osteoporotic # (Grade A to B evidence), improves lipid profile, decreased breast ca risk</td>
</tr>
<tr>
<td></td>
<td>• -ve: increased risk of DVT/PE, stroke mortality, hot flashes, leg cramps</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HRT: combined estrogen + progesterone (see Gynecology, GY35)</th>
<th>1st line in prevention of hip, nonvertebral, and vertebral # (Grade A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>For most women, risks &gt; benefits</td>
<td>Combined estrogen/progestin prevents hip, vertebral, total #</td>
</tr>
<tr>
<td></td>
<td>Increased risks of breast cancer, cardiovascular events, and DVT/PE</td>
</tr>
</tbody>
</table>

Before prescribing Calcitonin, remember to ask about fish allergies.
Osteomalacia and Rickets

- **rickets**: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue prior to epiphyseal closure (in childhood)
- **osteomalacia**: osteopenia with disordered calcification leading to a higher proportion of osteoid (unmineralized) tissue after epiphyseal closure (in adulthood)

**Etiology and Pathophysiology**

**Vitamin D Deficiency**
- deficient uptake or absorption
  - nutritional deficiency
  - malabsorption: post-gastrectomy, small bowel disease (e.g. Celiac sprue), pancreatic insufficiency
- defective 25-hydroxylation
  - liver disease
  - anticonvulsant therapy (phenytoin, carbamazepine, phenobarbital)
- loss of vitamin D binding protein
  - nephrotic syndrome
- defective 1-α-25 hydroxylation
  - hypoparathyroidism
  - renal failure
- pathophysiology: leads to secondary hyperparathyroidism and hypophosphatemia

**Mineralization Defect**
- abnormal matrix
  - osteogenesis imperfecta
  - fibrogenesis imperfecta
  - axial osteomalacia
- enzyme deficiency
  - hypophosphatasia (inadequate ALP bioactivity)
- presence of calcification inhibitors
  - bisphosphonates, aluminum, high dose fluoride, anticonvulsants

*Factors Necessary for Mineralization*
- Quantitatively and qualitatively normal osteoid formation
- Normal concentration of calcium and phosphate in ECF
- Adequate bioactivity of ALP
- Normal pH at site of calcification
- Absence of inhibitors of calcification
Table 36. Clinical Presentations of Rickets and Osteomalacia

<table>
<thead>
<tr>
<th>Rickets</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Skeletal pain and deformities, bow legged</td>
<td>• Not as dramatic</td>
</tr>
<tr>
<td>• Fracture susceptibility</td>
<td>• Diffuse skeletal pain</td>
</tr>
<tr>
<td>• Weakness and hypotonia</td>
<td>• Bone tenderness</td>
</tr>
<tr>
<td>• Disturbed growth</td>
<td>• Fractures</td>
</tr>
<tr>
<td>• Ricketic rosary (prominent costochondral junctions)</td>
<td>• Gait disturbances (waddling)</td>
</tr>
<tr>
<td>• Harrison’s groove (indentation of lower ribs)</td>
<td>• Proximal muscle weakness</td>
</tr>
<tr>
<td>• Hypocalcemia</td>
<td>• Hypotonia</td>
</tr>
</tbody>
</table>

Investigations

Table 37. Laboratory Findings in Osteomalacia and Rickets

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Serum Phosphate</th>
<th>Serum Calcium</th>
<th>Serum ALP</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin D deficiency</td>
<td>Decreased</td>
<td>Decreased to normal</td>
<td>Increased</td>
<td>Decreased calcitriol</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>Decreased</td>
<td>Normal</td>
<td>Decreased to normal</td>
<td></td>
</tr>
<tr>
<td>Proximal RTA</td>
<td>Decreased</td>
<td>Normal</td>
<td>Normal</td>
<td>Associated with hyperchloremic metabolic acidosis</td>
</tr>
</tbody>
</table>

Conditions associated with abnormal matrix formation

- radiologic findings
  - pseudofractures, fissures, narrow radiolucent lines – thought to be healed stress fractures or the result of erosion by arterial pulsation
  - loss of distinctness of vertebral body trabeculae; concavity of the vertebral bodies
  - changes due to secondary hyperparathyroidism: subperiosteal resorption of the phalanges, bone cysts, resorption of the distal ends of long bones
  - others: bowing of tibia, coxa profunda hip deformity
  - bone biopsy: usually not necessary but considered the gold standard for diagnosis

Treatment

- definitive treatment depends on the underlying cause
- vitamin D supplementation
- PO₄³⁻ supplements if low serum PO₄³⁻, Ca²⁺ supplements for isolated calcium deficiency
- bicarbonate if chronic metabolic acidosis

Renal Osteodystrophy

- changes to mineral metabolism and bone structure secondary to chronic kidney disease
- represents a mixture of four types of bone disease:
  - osteomalacia: low bone turnover combined with increased unmineralized bone (osteoid)
  - adynamic bone disease: low bone turnover due to excessive suppression of parathyroid gland
  - osteitis fibrosa cystica: increased bone turnover due to secondary hyperparathyroidism
  - mixed uremic osteodystrophy: both high and low bone turnover, characterized by marrow fibrosis and increased osteoid
- metastatic calcification secondary to hyperphosphatemia may occur

Pathophysiology

- metabolic bone disease secondary to chronic renal failure
- combination of hyperphosphatemia (inhibits 1,25(OH)₂-Vit D synthesis) and loss of renal mass (reduced 1-α-hydroxylase)

Clinical Features

- soft tissue calcifications → necrotic skin lesions if vessels involved
- osteodystrophy → generalized bone pain and fractures
- pruritus
- neuromuscular irritability and tetany may occur
- radiologic features of ostetitis fibrosa cystica, osteomalacia, osteosclerosis, osteoporosis

Investigations

- serum Ca²⁺ corrected for albumin, PO₄³⁻, PTH, ALP, ± imaging (x-ray, BMD), ± bone biopsy

Treatment

- prevention
  - maintenance of normal serum Ca²⁺ and PO₄³⁻ by restricting PO₄³⁻ intake to 1 g OD
  - Ca²⁺ supplements; PO₄³⁻ binding agents (calcium carbonate, aluminum hydroxide)
  - vitamin D with close monitoring to avoid hypercalcemia and metastatic calcification
Paget’s Disease of Bone

Definition
• a metabolic disease characterized by excessive bone destruction and repair

Epidemiology
• a common disease: 5% of the population, 10% of population >80 yr old
• consider Paget's disease of bone in older adults with ↑ ALP but normal GGT

Etiology and Pathophysiology
• postulated to be related to a slow progressing viral infection of osteoclasts, possibly paramyxovirus
• strong familial incidence
• initiated by increased osteoclastic activity leading to increased bone resorption; osteoblastic activity increases in response to produce new bone that is structurally abnormal and fragile

Differential Diagnosis
• primary bone lesions
  ▫ osteogenic sarcoma
  ▫ multiple myeloma
  ▫ fibrous dysplasia
• secondary bone lesions
  ▫ osteitis fibrosa cystica
  ▫ metastases

Clinical Features
• usually asymptomatic (routine x-ray finding or elevated ALP)
• severe bone pain (e.g. pelvis, femur, tibia) is often the presenting complaint
• skeletal deformities: bowed tibias, kyphosis, frequent fractures
• skull involvement: headaches, increased hat size, deafness
• increased warmth over involved bones due to increased vascularity
• high output CHF
• hypercalcemia with immobilization
• osteosarcoma

Investigations
• laboratory
  ▫ ↑↑ serum ALP (unless burnt out), Ca\(^{2+}\) normal or ↑, PO\(_4^{3-}\) normal
  ▫ urinary hydroxyproline ↑ (indicates resorption)
• imaging
  ▫ bone scan to evaluate the extent of disease
  ▫ confirmation on x-ray required to establish the diagnosis
  ▫ skeletal survey: involved bones are denser and expanded with cortical thickening
    ▪ initial lesion may be destructive and radiolucent
    ▪ multiple fissure fractures in long bones

Complications
• local
  ▫ fractures; osteoarthritis
  ▫ cranial nerve compression and palsies (e.g. deafness), spinal cord compression
  ▫ osteosarcoma/sarcomatous change in 1-3%
    ▪ indicated by marked bone pain, new lytic lesions and sudden increased ALP
• systemic
  ▫ hypercalcemia and nephrolithiasis
  ▫ high output CHF due to increased vascularity

Treatment
• symptomatic therapy (pain management)
• weight-bearing exercise
• adequate calcium and vitamin D intake to prevent development of secondary hyperparathyroidism
• treat medically if ALP >3x normal
  ▫ bisphosphonates, e.g. alendronate 40 mg PO OD x 6 mo OR risedronate 30 mg PO OD x 3 mo OR zoledronic acid 5 mg IV per yr
  ▫ calcitonin 50-100 U/d SC
• surgery for fractures, deformity, degenerative changes

Comparison of a Single Infusion of Zoledronic Acid with Risedronate for Paget’s Disease
NEJM 2005;353:898-908
Study: Two identical, randomized, double-blind, actively controlled trials (combined for analysis).
Patients: 357 men and women who were older than 30 yr of age and had radiologically confirmed Paget’s disease. All but 4 patients had alkaline phosphatase levels that were more than twice the upper limit of normal.
Intervention: One 15-min infusion of 5 mg of zoledronic acid compared with 60 d of oral risedronate (30 mg/d) with follow up at 6 mo.
Primary Outcome: Rate of therapeutic response at 6 mo, defined as a normalization of alkaline phosphatase levels or a reduction of at least 75% in the total alkaline phosphatase excess.
Results: At 6 mo, 96% of patients receiving zoledronic acid had a therapeutic response (169 of 176), as compared with 74.3% of patients receiving risedronate (127 of 171, p<0.001). Alkaline phosphatase levels normalized in 88.6% of patients in the zoledronic acid group and 57.9% of patients in the risedronate group (p<0.001). Zoledronic acid was associated with a shorter median time to a first therapeutic response (64 vs. 119 d, p<0.001).
Quality of life increased significantly from baseline at both 3 and 6 mo in the zoledronic acid group and differed significantly from those in the risedronate group at 3 mo. Pain scores improved in both groups. During post-trial follow-up (median, 198 d), 21 of 82 patients in the zoledronate group and 23 of 113 patients in the zoledronic acid group (p=0.001).
Conclusions: A single infusion of zoledronic acid produces more rapid, more complete, and more sustained responses in Paget’s disease than does daily treatment with risedronate.
Male Reproductive Endocrinology

Androgen Regulation

- negative feedback may occur by androgens directly or after conversion to estrogen
- testosterone (from Leydig cells) primarily involved in negative feedback on LH and GnRH, whereas inhibin (from Sertoli cells) suppresses FSH secretion

Tests of Testicular Function

- testicular size (lower limit = 4 cm x 2.5 cm)
- LH, FSH, total, bioavailable, and/or free testosterone
- human chorionic gonadotropin (hCG) stimulation test
  - assesses ability of Leydig cell to respond to gonadotropin
- semen analysis
  - semen volume, sperm concentration, morphology, and motility are the most commonly used parameters
- testicular biopsy
  - indicated with normal FSH and azoospermia/oligospermia

Hypogonadism and Infertility

- see Urology, U34
- deficiency in gametogenesis or testosterone production

Etiology

- causes include primary (testicular failure), secondary (hypothalamic-pituitary failure), and idiopathic
- primary hypogonadism is more common than secondary

Table 38. Classification and Features of Hypogonadism

<table>
<thead>
<tr>
<th>Hypogonadotropic Hypogonadism (Primary Hypogonadism)</th>
<th>Hypogonadotropic Hypogonadism (Secondary Hypogonadism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td></td>
</tr>
<tr>
<td>Primary testicular failure</td>
<td>Hypothalamic-pituitary axis failure</td>
</tr>
<tr>
<td>↑ LH and FSH, ↑ FSH:LH ratio</td>
<td>↓ LH + FSH (LH sometimes inappropriately normal)</td>
</tr>
<tr>
<td>↓ testosterone and sperm count</td>
<td>↓ testosterone and sperm count</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
</tr>
<tr>
<td>Congenital:</td>
<td></td>
</tr>
<tr>
<td>- Chromosomal defects (Klinefelter's, Noonan)</td>
<td></td>
</tr>
<tr>
<td>- Cryptorchidism</td>
<td></td>
</tr>
<tr>
<td>- Disorders of sexual development (DSD)</td>
<td></td>
</tr>
<tr>
<td>- Bilateral anorchia (vanishing testicle syndrome)</td>
<td></td>
</tr>
<tr>
<td>- Mystotic dystrophy</td>
<td></td>
</tr>
<tr>
<td>- Mutation of FSH or LH receptor gene</td>
<td></td>
</tr>
<tr>
<td>- Disorders of androgen synthesis</td>
<td></td>
</tr>
<tr>
<td>Germ cell defects</td>
<td></td>
</tr>
<tr>
<td>- Sertoli cell only syndrome</td>
<td></td>
</tr>
<tr>
<td>- Leydig cell aplasia/failure</td>
<td></td>
</tr>
<tr>
<td>Infection/Inflammation</td>
<td></td>
</tr>
<tr>
<td>- Orchitis – TB, lymphoma, mumps, leprosy</td>
<td></td>
</tr>
<tr>
<td>- Genital tract infection</td>
<td></td>
</tr>
<tr>
<td>Physical factors</td>
<td></td>
</tr>
<tr>
<td>- Trauma, heat, irradiation, testicular torsion,</td>
<td></td>
</tr>
<tr>
<td>- varicocele</td>
<td></td>
</tr>
<tr>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>- Marijuana, alcohol, chemotherapy,</td>
<td></td>
</tr>
<tr>
<td>- ketoconazole, glucocorticoid, spironolactone</td>
<td></td>
</tr>
<tr>
<td>- Autoimmune (antisperm antibodies)</td>
<td></td>
</tr>
<tr>
<td>- Chronic systemic diseases (AIDS)</td>
<td></td>
</tr>
<tr>
<td>- Idiopathic</td>
<td></td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
</tr>
<tr>
<td>Testicular size and consistency (soft/firm)</td>
<td>Testicular size and consistency (soft/firm)</td>
</tr>
<tr>
<td>Sperm count</td>
<td>Sperm count</td>
</tr>
<tr>
<td>LH, FSH, total, and/or bioavailable testosterone</td>
<td>LH, FSH, total, and/or bioavailable testosterone</td>
</tr>
<tr>
<td>hCG stimulation (mainly used in pediatrics)</td>
<td>Prolactin levels</td>
</tr>
<tr>
<td>Karyotype</td>
<td>MRI of hypothalamic-pituitary region</td>
</tr>
</tbody>
</table>

Two Distinct Features of Primary Hypogonadism

- The decrease in sperm count is affected to a greater extent than the decrease in serum testosterone level
- Likely to be associated with gynecomastia

Two Features of Secondary Hypogonadism

- Associated with an equivalent decrease in sperm count and serum testosterone
- Less likely to be associated with gynecomastia
**Treatment**
- Testosterone replacement (improve libido, muscle mass, strength, body hair growth, bone mass)
  - IM injection, transdermal testosterone patch/gel, oral
  - Side effects: acne, fluid retention, erythrocytosis, sleep apnea, benign prostatic hypertrophy, uncertain effects on cardiac events/mortality in older men
  - Contraindicated if history of prostate cancer, severe LUTS associated with BPH, uncontrolled or poorly controlled CHF
- GnRH agonist to restore fertility, if hypothalamic dysfunction with intact pituitary
  - Administered SC in pulsatile fashion using an external pump
- hCG ± recombinant follicular stimulating hormone (rFSH) can be used to restore fertility in cases of either hypothalamic or pituitary lesions
- Testicular sperm extraction (TESE) or microscopic sperm extraction (MICROTESE) – only if testicular tissues are not functioning

**Other Causes of Male Infertility**
- Hereditary disorders: Kartagener syndrome, cystic fibrosis
- Anatomy: hypospadias, retrograde ejaculation
- Obstruction: vasal occlusion, vasal aplasia, vasectomy, seminal vesicle disease
- Sexual dysfunction: erectile dysfunction, premature ejaculation, infrequent coitus
- Surgery: TURP, radical prostatectomy, orchiectomy

**DEFECTS IN ANDROGEN ACTION**

**Etiology**
- Complete androgen insensitivity (CAIS)
- Partial androgen insensitivity (PAIS)
- 5-α-reductase deficiency
- Mixed gonadal dysgenesis
- Defects in testosterone synthesis
- Infertile male syndrome
- Undervirilized fertile male syndrome

**Clinical Features**
- Depends on age of onset

**Table 39. Effects of Testosterone Deficiency**

<table>
<thead>
<tr>
<th>Time</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester in utero</td>
<td>Incomplete virilization of external genitalia (ambiguous genitalia)</td>
</tr>
<tr>
<td>Third Trimester in utero</td>
<td>Incomplete development of Wolffian ducts to form male internal genitalia (male pseudohermaphroditism)</td>
</tr>
<tr>
<td>Prepuberty</td>
<td>Micropenis, Cryptorchidism (failure of normal testicular descent)</td>
</tr>
<tr>
<td>Postpuberty</td>
<td>Incomplete pubertal maturation (high pitch voice, sparse pubic + axillary hair, absence of facial hair)</td>
</tr>
<tr>
<td></td>
<td>Eunuchoidal body habitus (greater growth of extremity long bones relative to axial bones)</td>
</tr>
<tr>
<td></td>
<td>Poor muscle development, reduced peak bone mass</td>
</tr>
<tr>
<td></td>
<td>Decrease in energy, mood, and libido</td>
</tr>
<tr>
<td></td>
<td>Fine wrinkles in corners of mouth and eyes</td>
</tr>
<tr>
<td></td>
<td>Decrease in pubic/axillary hair, hematocrit, muscle mass, strength, and BMD</td>
</tr>
</tbody>
</table>

Adapted from: UpToDate, 2010; Cecil’s Essentials of Medicine

**Treatment**
- Appropriate gender assignment in the newborn
- Hormone replacement or supplementation
- Psychological support
- Gonadectomy for cryptorchidism (due to increased risk for testicular cancer)
- Reduction mammoplasty for gynecomastia

**Erectile Dysfunction**

- See Urology, U30
Gynecomastia

Definition
- true gynecomastia refers to benign proliferation of the glandular component of the male breast, resulting in the formation of a concentric, rubbery, firm mass extending from the nipple(s)
- pseudogynecomastia or lipomastia refers to enlargement of soft adipose tissue, especially seen in obese individuals and does not warrant further evaluation

Etiology

Physiologic
- puberty
- elderly (involutional)
- neonatal (maternal hormone)

Pathologic
- endocrinopathies: primary or secondary hypogonadism, hyperthyroidism, extreme hyperprolactinemia, adrenal disease
- tumours: pituitary, adrenal, testicular, breast, ectopic production of hCG
- chronic diseases: cirrhosis, renal, malnutrition (with refeeding)
- drugs: estrogens and estrogen agonists, spironolactone, ketoconazole, cimetidine, digoxin, chemotherapy, marijuana, alcohol
- congenital/genetic: Klinefelter’s syndrome, androgen insensitivity
- other: idiopathic, familial

Pathophysiology
- hormonal imbalance due to increased estrogen activity (increased production, or increased availability of estrogen precursors for peripheral conversion to estrogen) or decreased androgen activity (decreased androgen production, binding of androgen to sex hormone binding globulin (SHBG), or androgen receptor blockage)

History
- recent change in breast characteristics
- trauma to testicles
- mumps
- alcohol and/or drug use
- FHx
- sexual dysfunction

Physical Exam
- signs of feminization
- breast
  - rule out red flags suggesting breast cancer: unilateral, eccentric, hard, or fixed mass, skin dimpling or retraction, and nipple discharge or crusting
  - gynecomastia occurs concentrically around nipple, is not fixed to underlying tissue, and no discrete mass is palpable
- genito-urinary exam
- stigmata of liver or thyroid disease

Investigations
- laboratory: serum TSH, PRL, LH, FSH, testosterone, estradiol, LFTs, creatinine, hCG (if hCG is elevated need to locate the primary tumour)
- CXR and CT of chest/abdomen/pelvis (to locate neoplasm)
- testicular U/S to rule out testicular mass
- MRI of hypothalamic-pituitary region if pituitary adenoma suspected

Treatment
- initial observation for most men with gynecomastia
- medical
  - correct the underlying disorder, discontinue responsible drug
  - androgens for hypogonadism
  - anti-estrogens: tamoxifen, clomiphene
- surgical
  - usually required for macromastia; gynecomastia present for >1 yr (fibrosis is unresponsive to medication); or failed medical treatment and for cosmetic purposes

Occurrence of Gynecomastia

<table>
<thead>
<tr>
<th>3 Peaks</th>
<th>% Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>60-90</td>
</tr>
<tr>
<td>Puberty</td>
<td>4-69</td>
</tr>
<tr>
<td>Ages 50-80</td>
<td>24-65</td>
</tr>
</tbody>
</table>
Female Reproductive Endocrinology

- see Gynecology, GY4

Paraneoplastic Syndrome

- clinical syndromes involving non-metastatic systemic effects that accompany malignant disease
- triggered by antibodies against neoplasm cross-reacting with normal tissue or by production of a physiologically active substance by the neoplasm
- commonly present with cancers of lung, breast, ovaries, or lymphatic system

Table 40. Clinical Presentation

<table>
<thead>
<tr>
<th>Syndrome Class</th>
<th>Symptoms/Syndrome</th>
<th>Associated Malignancies</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocrine</td>
<td>Cushing’s syndrome, SIADH, Hypercalcemia</td>
<td>Small-cell lung cancer, Pancreatic carcinoma, Neural tumours, Thymoma, Lung cancer</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Small-cell lung cancer, CNS malignancies</td>
<td>Antidiuretic hormone secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast carcinoma, Renal cell carcinoma, Multiple myeloma, Ovarian carcinoma</td>
<td>PTH-related protein, TGF-α, TNF secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hepatocellular carcinoma, Fibrosarcoma</td>
<td>Insulin or insulin-like substance secretion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pancreatic carcinoma, Gastric carcinoma</td>
<td>Serotonin, bradykinin secretion</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Lambert-Eaton myasthenic syndrome (LEMS)</td>
<td>Small-cell lung cancer, Thymoma</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td>Myasthenia gravis</td>
<td>Thymoma, Muscle weakness in limbs, Thymoma, Muscle weakness in limbs</td>
<td>Ab interferes with ACh release</td>
</tr>
<tr>
<td></td>
<td>Paraneoplastic limbic encephalitis</td>
<td>Small-cell lung cancer, Muscle weakness in limbs, Short-term memory loss</td>
<td>Unknown</td>
</tr>
<tr>
<td>Renal</td>
<td>Hypokalemic nephropathy</td>
<td>Small-cell lung cancer, Lymphoma</td>
<td>Ectopic ACTH and ACTH-like substance secretion</td>
</tr>
<tr>
<td></td>
<td>Nephrotic syndrome</td>
<td>Lymphoma, Melanomas, Muscle weakness in limbs, Muscle weakness in limbs</td>
<td>Immunocomplex sedimentation in nephrons</td>
</tr>
<tr>
<td>GI</td>
<td>Watery diarrhea</td>
<td>Medullary thyroid carcinomas, Gastric carcinoma</td>
<td>Prostaglandin secretion</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Erythrocytosis</td>
<td>Renal cell carcinoma, Hepatocellular carcinoma</td>
<td>EPO production</td>
</tr>
<tr>
<td>Rheumatologic</td>
<td>SLE</td>
<td>Lymphomas, Lung cancer, Breast carcinoma, Gonadal carcinoma</td>
<td>Anti-nuclear Ab production</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
<td>Breast carcinoma, Lung cancer, Uterine cancer</td>
<td>Anti-nuclear Ab production</td>
</tr>
</tbody>
</table>

Investigations
- CBC, electrolytes, creatinine, LFTs, ALP, ESR, CRP, serum/urine electrophoresis
- serum autoantibodies, lumbar puncture
- imaging: skeletal survey, CT, MRI, PET scan
- ± endoscopy

Treatment
- treat underlying tumour: surgery, radiation, chemotherapy
- treat immune-mediated disorder: IVIg, steroids, immunosuppressive drugs, plasmapheresis (reserved for patients with identifiable antibodies in serum)
### Diabetes Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanide</td>
<td>Sensitizes peripheral tissues to insulin</td>
<td>metformin</td>
<td>Glucomphage^®</td>
<td>Gluimetra^®</td>
<td>500 mg QD titrated to 2000 mg/d maximum</td>
<td>Useful in obese type 2 DM</td>
<td>GI upset (abdo discomfort, diarrhea), Lactic acidosis, Anorexia</td>
<td>↓ HbA1c 1.0-1.5%</td>
<td>Weight neutral</td>
</tr>
<tr>
<td></td>
<td>Increases glucose uptake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Decreases hepatic glucose production by simulation of hepatic AMP-activated protein kinase (AMPK)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Secretagogues</td>
<td>Stimulates insulin release from β-cells by causing K+ channel closure → depolarization → Ca2+ mediated insulin release</td>
<td>sulfonylureas:</td>
<td>glipizide</td>
<td>Diabeta^®</td>
<td>2.5-5.0 mg/d titrated to &gt;5 mg bid</td>
<td>Moderate to severe liver dysfunction</td>
<td>↓ HbA1c 0.8%</td>
<td>Hypoglycemia, Weight gain</td>
<td>↓ HbA1c 0.0%</td>
</tr>
<tr>
<td></td>
<td>Increases glucose uptake</td>
<td>gliclazide</td>
<td>Micronase^®</td>
<td>Glymase PreTab^®</td>
<td>40-160 mg bid</td>
<td>Moderate to severe liver dysfunction</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>glimepiride</td>
<td>Amaryl^®</td>
<td></td>
<td>1-8 mg OD</td>
<td>Moderate renal dysfunction</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>non-sulfonylureas:</td>
<td>repaglinide</td>
<td>Glucomort^®</td>
<td>0.5-4 mg tid</td>
<td>Short t1/2 of 1 h causes brief but rapid fall in insulin, therefore effective for post-prandial control</td>
<td>Absent</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>nateglinide</td>
<td>Starlix^®</td>
<td></td>
<td>60-120 mg OD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin Sensitizers (thiazolidinedione)</td>
<td>Sensitizes peripheral tissues to insulin</td>
<td>rosiglitazone</td>
<td>Avandia^®</td>
<td></td>
<td>2-8 mg OD</td>
<td>Rosiglitazone – indicated only in patients with type 2 DM for whom all other oral antidiabetic agents, in monotherapy or in combination, do not result in adequate glycemic control or are inappropriate due to contraindications or intolerance</td>
<td>Peripheral edema</td>
<td>CHF</td>
<td>↓ HbA1c 0.0%</td>
</tr>
<tr>
<td></td>
<td>Increases glucose uptake</td>
<td>pioglitazone</td>
<td>Actos^®</td>
<td></td>
<td>15-45 mg OD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitor of α-glucosidase</td>
<td>Inhibits carbohydrate GI absorption by inhibiting brush border α-glucosidase</td>
<td>acarbose</td>
<td>Glucoﬁl®</td>
<td></td>
<td>25 mg OD titrated to 100 mg tid</td>
<td>↑ postprandial hyperglycemia</td>
<td></td>
<td>Fatulence</td>
<td>Abdominal cramps</td>
</tr>
<tr>
<td>Dipeptidyl Peptidase-IV (DPP-IV) Inhibitor</td>
<td>Inhibits degradation of endogenous antiglycemic incretin hormones</td>
<td>sitagliptan</td>
<td>Januvia^®</td>
<td></td>
<td>100 mg OD</td>
<td>(DPP-IV) Inhibitor:</td>
<td>Nasopharyngitis</td>
<td>UrTi</td>
<td>↓ HbA1c 0.7%</td>
</tr>
<tr>
<td></td>
<td>Increases insulin secretion, inhibit glucagon release, and delay gastric emptying</td>
<td>saxagliptin</td>
<td>Onglyza™</td>
<td></td>
<td>2.5-5 mg OD</td>
<td>Type 1 DM</td>
<td>Headache</td>
<td>Pancreatitis</td>
<td>Weight neutral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>linagliptin</td>
<td>Trajenta™</td>
<td></td>
<td>5 mg OD</td>
<td>LDA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucagon-like Peptide (GLP)-1 Analogue</td>
<td>Binds to GLP-1 receptor to promote insulin release</td>
<td>Exenatide</td>
<td>Byetta™</td>
<td></td>
<td>5-10 µg SC bid 1 h before meals</td>
<td>Type 1 DM</td>
<td></td>
<td>N/L diarrhea</td>
<td>↓ HbA1c 1.0%</td>
</tr>
<tr>
<td></td>
<td>Insulinotropic effect suppressed as plasma glucose &lt;4 mmol/L</td>
<td>Linagliotide</td>
<td>Victoza™</td>
<td></td>
<td>0.6-1.8 mg OD SC</td>
<td>Type 1 DM</td>
<td></td>
<td>Dizziness, headache</td>
<td></td>
</tr>
</tbody>
</table>

For insulin formulations see Table 9, E9
### Dyslipidemia Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMG-CoA Reductase Inhibitor</td>
<td><em>Inhibits cholesterol biosynthesis, ↓LDL synthesis, ↑LDL clearance, modest ↑HDL, ↓VLDL</em></td>
<td>atorvastatin</td>
<td>Lipitor®</td>
<td>10-80 mg/d, 20-80 mg/d, 20-30 mg/d, 10-40 mg/d, 5-40 mg/d, 10-80 mg/d</td>
<td>• 1st line monotherapy</td>
<td>• Active liver disease</td>
<td>• GI symptoms</td>
<td>• Rash, pruritus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fluvastatin</td>
<td>Lescol®</td>
<td></td>
<td></td>
<td></td>
<td>• ↑ liver enzymes</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pravastatin</td>
<td>Mivacor®</td>
<td></td>
<td></td>
<td></td>
<td>• Myasthenia (↑ risk if combined with fibrates)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>rosuvastatin</td>
<td>Pravachol®</td>
<td></td>
<td></td>
<td></td>
<td>• Rhabdomyolysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>simvastatin</td>
<td>Crestor®</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Zocor®</td>
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</tr>
<tr>
<td>Fibrates</td>
<td><em>Upregulate lipoprotein lipase + apo A1, ↓VLDL, ↓TG, modest ↓HDL, decreased clearance of HDL</em></td>
<td>bezafibrate</td>
<td>Bezalip®</td>
<td>400 mg/d, 480-200 mg/d, 600-1200 mg/d</td>
<td>• Used for ↑TG, hyperchylomicronemia</td>
<td>• Hepatic disease</td>
<td>• GI upset</td>
<td>• Skin rashes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>fenofibrate</td>
<td>Lipidil®</td>
<td></td>
<td></td>
<td></td>
<td>• Renal disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>gemfibrozil</td>
<td>Lopid®</td>
<td></td>
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</tr>
<tr>
<td>Niacin</td>
<td><em>Inhibits secretion of hepatic VLDL via lipoprotein lipase (LPL) pathway → decreased VLDL and LDL, modest ↓HDL</em></td>
<td>nicotinic acid</td>
<td>Niaspan®</td>
<td>0.5-2 g/d, 1-3 g/d</td>
<td>• Used for ↑LDL, ↑VLDL</td>
<td>• Hyperemesis</td>
<td>• Generalized flushing</td>
<td>• Abnormal liver enzymes</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>generic niacin</td>
<td></td>
<td></td>
<td></td>
<td>• Pruritus</td>
<td>• IGT</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bile Acid Sequestrants</td>
<td><em>Resins that bind bile acids in intestinal lumen and prevent absorption thereby ↓LDL</em></td>
<td>cholestyramine</td>
<td>Questran®</td>
<td>2-24 g/d</td>
<td>• Used for ↑LDL</td>
<td>• Complete biliary obstruction</td>
<td>• Constipation</td>
<td>• Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Hypersensitivity</td>
<td>• Fatality</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Cholesterol Absorption Inhibitors</td>
<td><em>Inhibits cholesterol absorption at the small intestine brush border</em></td>
<td>ezetimibe</td>
<td>Ezetrol®</td>
<td>10 mg/d</td>
<td>• Used for ↑LDL, apo B</td>
<td>• Hypersensitivity</td>
<td>• Fatigue</td>
<td>• Pharyngitis</td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

### Thyroid Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid Agent (thionamides)</td>
<td><em>Decreases thyroid hormone production by inhibiting iodine and peroxidase from interacting with thyroglobulin to form T3 and T4, PTU also interferes with conversion of T4 to T3</em></td>
<td>propylthiouracil (PTU)</td>
<td>Propyl-Thyacil®</td>
<td></td>
<td>Start 100 mg PO bid, then adjust accordingly</td>
<td>• Hyperthyroidism</td>
<td>• N/V</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>methimazole (MMI)</td>
<td>Tapazole®</td>
<td></td>
<td>Start 5-20 mg PO OD, then adjust accordingly, Up to 60 mg OD may be required</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid Hormone</td>
<td><em>Synthetic form of thyroxine (T4)</em></td>
<td>levothyroxine</td>
<td>Synthroid®</td>
<td>0.05-2.0 mg/d, usually 1.8 x weight (kg) is dose in micrograms In elderly patients start at 0.025 mg/d</td>
<td>• Hypothyroidism</td>
<td>• Recent MI, thyrotoxicosis</td>
<td>• If wrong dosing: symptoms of hypothyroidism or hyperthyroidism</td>
<td>• Skin rash from dye in pill</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liothyronine</td>
<td>Eltroxin®</td>
<td>Levaxyl®</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithyroid Agent Radiopharmaceutical</td>
<td><em>Radioactive isotope of iodine that is incorporated into the thyroid gland irradiating the area and destroying local glandular tissue</em></td>
<td>sodium iodide 1-131</td>
<td>Iodotope®</td>
<td>Dose corrected for 24 h radioactive iodine uptake Hyperthyroidism 4-12 mCi Thyroid Ca 50-150 mCi</td>
<td>• Hyperthyroidism</td>
<td>• N/V</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

In summary, the dyslipidemia medications listed include HMG-CoA reductase inhibitors, fibrates, niacin, bile acid sequestrants, and cholesterol absorption inhibitors. The thyroid medications include antithyroid agents (thionamides), thyroid hormones, and antithyroid agents radiopharmaceuticals.
<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bisphosphonates</td>
<td>• Inhibits osteoclast-mediated bone resorption</td>
<td>alendronate</td>
<td>Fosamax®</td>
<td></td>
<td>Osteoporosis: 5-10 mg OD 70 mg once weekly Paget’s: 40 mg OD for 6 mo</td>
<td>• Prevention of postmenopausal osteoporosis • Treatment of osteoporosis • Glucocorticoid-induced osteoporosis • Paget’s disease</td>
<td>• Esophageal stricture or achalasia (oral) • Unable to stand or sit upright for &gt; 30 min (oral) • Hypersensitivity • Hypercalcemia • Renal insufficiency</td>
<td>• GI • MSK pain • Headache • Osteonecrosis of the jaw</td>
</tr>
<tr>
<td></td>
<td></td>
<td>risedronate</td>
<td>Actonel®</td>
<td></td>
<td>Osteoporosis: 5 mg OD 35 mg once weekly 150 mg once monthly Paget’s: 30 mg OD for 2 mo</td>
<td>• Treatment and prevention of postmenopausal osteoporosis • Treatment and prevention of glucocorticoid-induced osteoporosis • Paget’s disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>etidronate</td>
<td>Didronel®</td>
<td>Paget’s: 5-10 mg /kg OD x 6 mo</td>
<td>• Symptomatic Paget’s disease • Prevention and treatment of heterotopic ossification after total hip replacement or spinal cord injury</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ibandronate</td>
<td>Boniva®</td>
<td>2.5 mg OD or 150 mg once monthly</td>
<td>• Treatment and prevention of postmenopausal osteoporosis (US only)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>pamidronate</td>
<td>Aredia®</td>
<td>Hypercalcemia of malignancy 60-80 mg IV over 2-24 h Wait at least 7 d before considering retreatment</td>
<td>• Hypercalcemia of malignancy • Paget’s disease • Osteolytic bone metastases of breast cancer • Osteolytic lesions of multiple myeloma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>zoledronate</td>
<td>Zometa® Aclasta®</td>
<td>5 mg IV once yearly IV</td>
<td>• Treatment of osteoporosis • Hypercalcemia of malignancy • Treatment and prevention of skeletal complications related to cancer</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective Estrogen Receptor Modulators</td>
<td>• Decreases resorption of bone through binding to estrogen receptors</td>
<td>raloxifene</td>
<td>Evista®</td>
<td></td>
<td>60 mg OD</td>
<td>• Treatment and prevention of postmenopausal osteoporosis (2nd line)</td>
<td>• Lactation • Pregnancy • Active or past history of DVT, PE, or retinal vein thrombosis</td>
<td>• Hot flushes • Leg cramps • Increased risk of fatal stroke, venous thromboembolism</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>• Inhibits osteoclast-mediated bone resorption</td>
<td>calcitonin</td>
<td>Miacalcin®</td>
<td></td>
<td>One spray (200 IU) per day, alternating nostrils</td>
<td>• Treatment of postmenopausal osteoporosis, greater than 5 yr postmenopause</td>
<td>• Clinical allergy to salmon-calcitonin</td>
<td>• Rhinitis • Epistaxis • Sinusitis • Nasal dryness</td>
</tr>
<tr>
<td>Anti-RANKL Monoclonal Ab</td>
<td>• Inhibits RANKL (osteoclast differentiating factor) → inhibit osteoclast formation and decrease bone resorption</td>
<td>denosumab</td>
<td>Prolia™ Xgeva™</td>
<td></td>
<td>60 mg SC q6mo</td>
<td>• Treatment of postmenopausal women at high risk of fracture • Prevent skeletal-related events in patients with bone metastases from solid tumours</td>
<td>• Hypocalcemia</td>
<td>• Fatigue/headache • Dermatitis/rash • Hypophosphatemia/Hypocalcemia • Hypercholesterolaemia • GI discomfort</td>
</tr>
<tr>
<td>PTH</td>
<td>• Stimulates new bone formation by preferential stimulation of osteoblastic activity over osteoclastic activity</td>
<td>teriparatide</td>
<td>Forteo®</td>
<td></td>
<td>20 μg SC OD x 18-24 mo</td>
<td>• Treatment of postmenopausal women with osteoporosis who are at high risk for fracture • Treatment of men with primary or hypogonadal osteoporosis who are at high risk for fracture</td>
<td>• Paget’s disease • Prior external beam or implant radiation therapy involving the skeleton • Bone metastases • Metabolic bone diseases other than osteoporosis</td>
<td>• Orthostatic hypotension • Hypercalcemia • Dizziness • Leg cramps</td>
</tr>
</tbody>
</table>
### Metabolic Bone Disease Medications (continued)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mechanism of Action</th>
<th>Generic Drug Name</th>
<th>Canada Name</th>
<th>US Name (if different)</th>
<th>Dosing</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>• Inhibits PTH secretion</td>
<td>Calcium carbonate</td>
<td>Canada Name</td>
<td>US Name (if different)</td>
<td>1200 mg/d (including diet) Divided in 3 doses</td>
<td>• Osteopenia • Osteoporosis • Prevention of metabolic bone disease</td>
<td>• Caution with renal stones</td>
<td>• Vomiting • Constipation • Dry mouth</td>
</tr>
<tr>
<td>Vitamin D</td>
<td>• Regulation of calcium and phosphate homeostasis</td>
<td>cholecalciferol (vitamin D3)</td>
<td>Canada Name</td>
<td>US Name (if different)</td>
<td>800 - 2000 IU/d</td>
<td>• Osteopenia • Osteoporosis • Prevention of metabolic bone disease</td>
<td>Caution in patients on digoxin (risk of hypercalcemia which may precipitate arrhythmia)</td>
<td>Hypercalcemia • Headache • N/V • Constipation</td>
</tr>
<tr>
<td>Calcium</td>
<td>• Inhibits PTH secretion</td>
<td>ergocalciferol (vitamin D2)</td>
<td>Canada Name</td>
<td>US Name (if different)</td>
<td>50,000 IU/wk</td>
<td>• Osteoporosis in patients with liver dysfunction, refractory rickets, hyperparathyroidism</td>
<td>Hypercalcemia • Malabsorption syndrome • Decreased renal function</td>
<td></td>
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<tr>
<td>Vitamin D</td>
<td>• Regulation of calcium and phosphate homeostasis</td>
<td>calcitriol (1,25(OH)2-D)</td>
<td>Canada Name</td>
<td>US Name (if different)</td>
<td>Start 0.25 µg/d Titrate up by 0.25 µg/d at 2-4 wk intervals to 0.5-2 µg/d</td>
<td>• Hypocalcemia and osteodystrophy in patients with chronic renal failure on dialysis</td>
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</tbody>
</table>

### Adrenal Medications

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Mineralocorticoid Activity</th>
<th>Generic Drug Name</th>
<th>Potency (Relative to Cortisol)</th>
<th>Equivalent Dose (mg)</th>
<th>Duration of Action (t1/2 in h)</th>
<th>Dosing</th>
<th>Comments</th>
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</thead>
<tbody>
<tr>
<td>Hydrocortisone</td>
<td>Yes</td>
<td>Cortef Solu-Cortef</td>
<td>1.0</td>
<td>20</td>
<td>8</td>
<td>Adrenal Crisis: 50-100 mg IV bolus, then 50-100 mg q8h (continuous infusion x 24-48 h) PO once stable (50 mg q8h x 48 h, then taper over 14 d) Chronic AI: 15-20 mg PO OD (2/3 AM, 1/3 PM)</td>
<td>In high doses, mineralocorticoid side effects may emerge (salt + water retention, ECF volume expansion, HTN, low K+ metabolic alkalosis)</td>
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<tr>
<td>Cortisone Acetate</td>
<td>Yes</td>
<td>Cortisone Acetate</td>
<td>0.8</td>
<td>25</td>
<td>Oral = 8 IM = 18</td>
<td>Adrenal Crisis: 75-300 mg/d PO/IM divided q12-24h Chronic AI: 25 mg/d</td>
<td>Pro-drug which is converted to active form as hydrocortisone • High doses can result in mineralocorticoid side effects (see above)</td>
</tr>
<tr>
<td>Prednisone</td>
<td>No</td>
<td>Prednisone</td>
<td>4</td>
<td>5</td>
<td>16-36</td>
<td>Adrenal Crisis: 15-60 mg/d PO qd or divided bid/qid Chronic AI: 5 mg daily</td>
<td>Pro-drug which is converted to active form as prednisolone</td>
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<tr>
<td>Dexamethasone</td>
<td>No</td>
<td>Dexamethasone</td>
<td>30</td>
<td>0.7</td>
<td>36-54</td>
<td>Adrenal Crisis: 4 mg IV, repeat q2-6h if necessary</td>
<td>Used for undiagnosed adrenal insufficiency (does not interfere with measurement of serum cortisol levels)</td>
</tr>
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</table>
## Landmark Endocrinology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
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<tbody>
<tr>
<td><strong>DIABETES</strong></td>
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<tr>
<td>ACCORD</td>
<td>NEJM 2008; 358:2560-72</td>
<td>Compared with standard therapy the use of intensive therapy to target normal HbA1c levels (&lt;6%) for 3.5 yr increased mortality and did not significantly reduce major cardiovascular events.</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>NEJM 2008; 358:2545-59</td>
<td>Intensive glucose control that lowered the HbA1c value to 6.5% reduced the incidence of nephropathy but did not significantly reduce major macrovascular events, death from cardiovascular events, or death from any cause; hypoglycemia was more common in the intensive control group.</td>
</tr>
<tr>
<td>BARI-2D</td>
<td>NEJM 2009; 360:2503-15</td>
<td>In patients with both type 2 DM and CAD no significant difference was found in the rates of death and major cardiovascular events in patients undergoing prompt revascularization and those undergoing medical therapy or between strategies of insulin sensitization and insulin.</td>
</tr>
<tr>
<td>DCCT</td>
<td>NEJM 1993; 329:977-86</td>
<td>Intensive blood glucose control delayed the onset and reduced the progression of microvascular complications (retinopathy, nephropathy, and neuropathy) in type 1 DM.</td>
</tr>
<tr>
<td>EDIC</td>
<td>NEJM 2005; 353:2844-53</td>
<td>Compared with conventional therapy intensive DM therapy early on without macrovascular disease (goal HbA1c &lt;6.05%) has long-term beneficial effects on the risk of cardiovascular disease in patients with type 1 DM.</td>
</tr>
<tr>
<td>Look.AHEAD</td>
<td>NEJM 2013; 369:145-54</td>
<td>Moderate weight loss (&lt;7% BW) and increased exercise are not associated with reduction in CVD and its complications among overweight or obese patients with type 2 DM.</td>
</tr>
<tr>
<td>NAVIGATOR</td>
<td>NEJM 2010; 362:1463-90</td>
<td>In patients with impaired glucose tolerance, nateglinide did not reduce progression to DM or risk of cardiovascular events while valsartan only reduced progression to DM.</td>
</tr>
<tr>
<td>PREDIMED</td>
<td>NEJM 2013; 368:1279-90</td>
<td>A Mediterranean diet with extra-virgin olive oil or nuts reduces rates of MI, CVA, or CV death in those at high risk for CV disease (outcome was driven by reduction in rates of CVA).</td>
</tr>
<tr>
<td>Steno-2</td>
<td>NEJM 2008; 358:580-91</td>
<td>In at-risk patients with type 2 DM intensive intervention with multiple drug combinations and behaviour modification had sustained significant beneficial effects with respect to vascular complications and mortality; multifactorial intervention is critical in the management of type 2 DM.</td>
</tr>
<tr>
<td>UKPDS Extension</td>
<td>NEJM 2008; 359:1577-89</td>
<td>Continued risk reduction in microvascular risk and emergent risk reductions for MI and death from any cause 10 yr post UKPDS trial follow up in type 2 DM.</td>
</tr>
<tr>
<td>VADT</td>
<td>NEJM 2009; 360:1-11</td>
<td>In patients with longstanding poorly controlled type 2 DM intensive glucose control had no significant effect on the rates of major cardiovascular events, death, or microvascular complications; adverse events, predominantly hypoglycemia, were more common in the intensive control group.</td>
</tr>
<tr>
<td><strong>LIPIDS</strong></td>
<td></td>
<td></td>
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<tr>
<td>4S</td>
<td>Lancet 1994; 344:1383-89</td>
<td>In patients with angina or previous MI and high total cholesterol simvastatin reduced: all-cause mortality, fatal and nonfatal coronary events, and need for coronary artery bypass surgery or angioplasty.</td>
</tr>
<tr>
<td>FIELD</td>
<td>Lancet 2005; 366:1849-61</td>
<td>In patients with type 2 DM not previously on statin therapy fenofibrate did not significantly reduce the risk of the primary outcome of coronary events; it did reduce non-fatal MI and revascularizations.</td>
</tr>
<tr>
<td>HPS</td>
<td>Lancet 2002; 360:7-22</td>
<td>In high-risk patients with various cholesterol values simvastatin reduced all-cause mortality, coronary deaths, and major vascular events.</td>
</tr>
<tr>
<td>Jupiter</td>
<td>NEJM 2008; 359:2195-207</td>
<td>Rosuvastatin significantly reduced the incidence of major cardiovascular events in patients with elevated high-sensitivity CRP levels and no hyperlipidemia.</td>
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<tr>
<td>TNT</td>
<td>NEJM 2005; 352:1425-35</td>
<td>Lipid-lowering therapy with atorvastatin 80 mg/d in patients with stable CHD provides clinical benefit beyond atorvastatin 10 mg/d.</td>
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<tr>
<td>Acronyms</td>
<td>Definitions</td>
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<td>--------------------------</td>
<td>-----------------------------------------------------------------------------</td>
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<tr>
<td>AAA</td>
<td>abdominal aortic aneurysm</td>
<td></td>
</tr>
<tr>
<td>ACR</td>
<td>albumin:creatinine ratio</td>
<td></td>
</tr>
<tr>
<td>AIN</td>
<td>anal intraepithelial neoplasia</td>
<td></td>
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<tr>
<td>AMC</td>
<td>another medical condition</td>
<td></td>
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<tr>
<td>AKI</td>
<td>acute kidney injury</td>
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<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>ABG</td>
<td>arterial blood gas</td>
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</tr>
<tr>
<td>ALR</td>
<td>absolute reduction</td>
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<tr>
<td>BPPV</td>
<td>benign paroxysmal positional vertigo</td>
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<tr>
<td>CA</td>
<td>cancer</td>
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<tr>
<td>CABG</td>
<td>coronary artery bypass graft</td>
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<td>CAD</td>
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<tr>
<td>CBT</td>
<td>cognitive behavioural therapy</td>
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<tr>
<td>CF</td>
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<tr>
<td>CHF</td>
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<tr>
<td>CPAP</td>
<td>continuous positive airway</td>
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<tr>
<td>CRP</td>
<td>cytokine, interleukin receptors</td>
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<tr>
<td>CRF</td>
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<tr>
<td>DHP</td>
<td>dihydropyridine</td>
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<tr>
<td>DMPP</td>
<td>depot medroxyprogesterone</td>
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<td>DRE</td>
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<td>DS</td>
<td>double strength</td>
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<td>ED</td>
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<tr>
<td>FAP</td>
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<td>Fbg</td>
<td>fasting blood glucose</td>
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<td>FG</td>
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<td>FOG</td>
<td>fecal occult blood test</td>
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<tr>
<td>FRS</td>
<td>Framingham Risk Score</td>
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<td>GAD</td>
<td>generalized anxiety disorder</td>
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<td>GERD</td>
<td>gastroesophageal reflux disease</td>
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<td>GITT</td>
<td>gastric intravenous test</td>
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<td>HART</td>
<td>highly active anti-retroviral therapy</td>
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<td>HDL-C</td>
<td>high-density lipoprotein cholesterol</td>
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<td>HNPCC</td>
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<td>HSIL</td>
<td>high-squamous cell</td>
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<tr>
<td>ICS</td>
<td>inhaled corticosteroids</td>
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<td>IFG</td>
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<td>IGT</td>
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<td>IHP</td>
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<td>IRH</td>
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<td>intravenous injection</td>
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<td>KUB</td>
<td>kidneys, ureter, bladder x-ray</td>
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<td>LBL-C</td>
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<td>LVE</td>
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<td>LVH</td>
<td>left ventricle hypertrophy</td>
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<td>MDC</td>
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<td>monoamine oxidase inhibitor</td>
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<td>monounsaturated fatty acids</td>
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<tr>
<td>OCPD</td>
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<td>PCOS</td>
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<td>PID</td>
<td>perineal inflammatory disease</td>
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<td>premenstrual syndrome</td>
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<td>PNT</td>
<td>paroxysmal nocturnal dyspnea</td>
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<td>PPD</td>
<td>pulmonary insufficiency</td>
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<td>PUD</td>
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<td>polyunsaturated fatty acids</td>
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<td>PVD</td>
<td>peripheral vascular disease</td>
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<td>rheumatoid arthritis</td>
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<td>RCT</td>
<td>randomized controlled trial</td>
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<td>SAH</td>
<td>subarachnoid hemorrhage</td>
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<tr>
<td>SDR</td>
<td>serotonin dopamine reuptake inhibitor</td>
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<td>SREM</td>
<td>selective estrogen receptor</td>
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<td>SIDS</td>
<td>sudden infant death syndrome</td>
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<tr>
<td>SLE</td>
<td>systemic lupus erythematosis</td>
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<tr>
<td>SNRI</td>
<td>serotonin norepinephrine</td>
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<tr>
<td>SOB</td>
<td>shortness of breath</td>
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<tr>
<td>SSR</td>
<td>selective serotonin reuptake inhibitor</td>
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<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
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<td>TCA</td>
<td>tricyclic antidepressant</td>
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<td>tympanic membrane</td>
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<td>temporomandibular joint</td>
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<tr>
<td>TURP</td>
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<td>UCS</td>
<td>ureteral colitis</td>
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<tr>
<td>UTC</td>
<td>urinary tract infection</td>
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<tr>
<td>UTV</td>
<td>upper respiratory tract infection</td>
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<tr>
<td>VAIN</td>
<td>vaginal intraepithelial neoplasia</td>
<td></td>
</tr>
<tr>
<td>VIB</td>
<td>vertebrobasilar insufficiency</td>
<td></td>
</tr>
<tr>
<td>VIB</td>
<td>vertebrobasilar insufficiency</td>
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<tr>
<td>WISS</td>
<td>Workplace Safety and Insurance Board</td>
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</table>

**References**
Four Principles of Family Medicine

College of Family Physicians of Canada Guidelines
1. The family physician is a skilled clinician
   • in diagnosing and managing diseases common to the population served
   • recognizes importance of early diagnosis of serious life-threatening illnesses
2. Family medicine is a community-based discipline
   • provides information and access to community services
   • responds/adapts to changing needs and circumstances of the community
3. The family physician is a resource to a defined practice population
   • serves as a health resource
   • advocates for public policy to promote health
4. The patient-physician relationship is central to the role of the family physician
   • committed to the person, not just the disease
   • promotes continuity of patient care

Periodic Health Examination

• Canadian Task Force on Preventive Health Care established in 1976, first published in 1979
• mandate: to develop and disseminate clinical practice guidelines for primary and preventive care
• recommendations are based on systematic analysis of scientific evidence
  • most notable recommendation is the abolition of the annual physical exam; replaced by the PHE

Purpose of the Periodic Health Examination

• primary prevention: identify risk factors for common diseases; counsel patients to promote healthy behaviour
• secondary prevention: presymptomatic detection of disease to allow early treatment and to prevent disease progression
• update clinical data
• enhance patient-physician relationship

Classification of Recommendations (GRADE, 2011)

Strength of Recommendation
• strong: high level of confidence that desirable effects outweigh undesirable effects (strong recommendation for an intervention) or that the undesirable effects outweigh desirable effects (strong recommendation against an intervention)
  • implies that most individuals will be best served by the recommended course of action
• weak: desirable effects probably outweigh the undesirable effects (weak recommendation for an intervention) or undesirable effects probably outweigh the desirable effects (weak recommendation against an intervention); uncertainty exists
  • implies that most people would want the recommended course of action but that many would not
  • different choices will be appropriate for different individuals, patients require support in reaching a management decision consistent with his/her values and preferences

Quality of Evidence
• high: high level of confidence that true effect lies close to the estimate of the effect
• moderate: true effect likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
• low or very low: true effect may be substantially different from the estimate of the effect
Table 1. Periodic Health Exam

<table>
<thead>
<tr>
<th>General Population</th>
<th>Special Population</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DISCUSSION</strong></td>
<td><strong>Pediatrics:</strong></td>
</tr>
<tr>
<td>• Dental hygiene (community fluoridation, brushing, flossing) (A)</td>
<td>Home visits for high risk families (A), inquiry into developmental milestones (B)</td>
</tr>
<tr>
<td>• Noise control and hearing protection (A)</td>
<td>Adolescents: Counsel on sexual activity and contraceptive methods (B), Counsel to prevent smoking initiation (B)</td>
</tr>
<tr>
<td>• Screen for poverty</td>
<td>Perimenopausal Woman (Adults &gt;50): Assess for risk factors for osteoporosis and fracture (A), Counsel on osteoporosis, Counsel on risks/benefits of hormone replacement therapy (B)</td>
</tr>
<tr>
<td>• Smokers: counsel on smoking cessation, provide:</td>
<td>Adults &gt;65: Follow-up on caregiver concern of cognitive impairment (A), Multidisciplinary post-fall assessment (A)</td>
</tr>
<tr>
<td>• Nicotine replacement therapy (A)</td>
<td>First-Degree Relative with Melanoma: Full body skin exam (B)</td>
</tr>
<tr>
<td>• Referral to smoking cessation program (B)</td>
<td></td>
</tr>
<tr>
<td>• Dietary advice on leafy green vegetables and fruits (B)</td>
<td></td>
</tr>
<tr>
<td>• Seat belt use (B)</td>
<td></td>
</tr>
<tr>
<td>• Injury prevention (bicycle helmets, smoke detectors) (B)</td>
<td></td>
</tr>
<tr>
<td>• Moderate physical activity (B)</td>
<td></td>
</tr>
<tr>
<td>• Avoid sun exposure and wear protective clothing (B)</td>
<td></td>
</tr>
<tr>
<td>• Problem drinking screening and counselling (B)</td>
<td></td>
</tr>
<tr>
<td>• Counselling to protect against STIs (B)</td>
<td></td>
</tr>
<tr>
<td>• Nutritional counselling and dietary advice on fat and cholesterol (B)</td>
<td></td>
</tr>
<tr>
<td>• Dietary advice on calcium and vitamin D requirements (B)</td>
<td></td>
</tr>
</tbody>
</table>

| PHYSICAL           |                             |
| • Blood pressure measurement at primary care visits, using techniques described in CHIEP guidelines (strong recommendation; moderate quality evidence) |                             |
| • BMI measurement in obese adults (B) |                             |

| TESTS               |                             |
| • See recommendations below for age and gender specific screening for diabetes, dyslipidemia, hypertension and cancer screening (colon, prostate, cervical and breast) | Routine hemoglobin for high risk infants (B), Blood lead screening of high risk infants (B) |
| • Folic acid supplementation to women of child-bearing age (A) | STB High Risk Groups: Mantoux skin testing (A) |
| • Pharmacologic treatment of HTN with dBP > 90 mmHg (adults age 21-64, elderly specific subgroup) (A) | STI High Risk Groups: Voluntary HIV antibody screening (A) Chlamydia screening in women (B) Syphilis screen (A) |
| • Varicella vaccine for children age 1-12 and susceptible adolescents/adults (A) | Syphilis Risk Group: VDLR test (A) |
| • Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B) |                             |
| • Tetanus vaccine: routine booster q10yr if had 1st series (A) |                             |
| • Pertussis vaccine: adults < 65 should receive one booster given as Tdap– Adacel® or Boostrix® (A) |                             |
| • Herpes zoster vaccine for adults ≥60 |                             |

| THERAPY             |                             |
| • Folic acid supplementation to women of child-bearing age (A) | Pediatrics: Routine immunizations (A), Hepatitis B, HPV and Meningococcal immunizations are offered in schools in most Canadian provinces |
| • Pharmacologic treatment of HTN with dBP > 90 mmHg (adults age 21-64, elderly specific subgroup) (A) | Influenza High Risk Groups: Outreach strategies for vaccination (A), annual immunization (B), now recommended for all |
| • Varicella vaccine for children age 1-12 and susceptible adolescents/adults (A) |                             |
| • Rubella vaccine for all non-pregnant women of child-bearing age unless there is proof of immunity via immunization records or serology (B) |                             |
| • Tetanus vaccine: routine booster q10yr if had 1st series (A) |                             |
| • Pertussis vaccine: adults < 65 should receive one booster given as Tdap– Adacel® or Boostrix® (A) |                             |
| • Herpes zoster vaccine for adults ≥60 |                             |

Breast Cancer Screening Guidelines

2011 Recommendations on Screening for Breast Cancer in Average-Risk Women (The Canadian Task Force on Preventive Health Care)

- average-risk women: women age 40-74 with no personal history of breast cancer, history of breast cancer in 1st degree relatives, known mutations of the BRCA1/BRCA2 genes or previous exposures of the chest wall to radiation

Mammography
- age 40-49: routine screening with mammography not recommended (weak recommendation - moderate quality evidence)
- age 50-74: routine screening q2-3yr (age 50-69: weak recommendation; moderate quality evidence, age 70-74: weak recommendation; low quality evidence)
- age 75+: screen if benefits outweigh harm, must take overall health into account

Magnetic Resonance Imaging
- no routine screening with MRI scans (weak recommendation - low quality evidence)
Clinical Breast Examination
• no routine CBE alone or in conjunction with mammography to screen for breast cancer (weak recommendation - low quality evidence)

Breast Self-Examination
• recommend not advising women to routinely practice breast self-examination
• for more information on benign breast lesions and breast cancer, see General Surgery, GS56

Colorectal Cancer Screening Guidelines
• recommendations for average risk individuals (asymptomatic, no family history of UC, polyps, or CRC)
• average risk testing should begin at age 50, but assessment for risk factors should begin earlier to identify high-risk individuals
   • Canadian Association of Gastroenterology (2010)
     • FOBT q1-2yr. Note: high sensitivity FOBT or FIT (fecal immunochemical testing) are recommended
     • flexible sigmoidoscopy q10yr
     • colonoscopy q10yr
   • no screening after age 75 is recommended for average risk patients, but it may be assessed on an individual basis for ages 76-85
• for more information on colorectal neoplasms, see General Surgery, GS34

Figure 1. Approach to higher risk screening
AAPP = attenuated adenomatous polyposis; FAP = familial adenomatous polyposis; HNPCC = hereditary nonpolyposis colorectal cancer; 1st degree relatives: parents, siblings, children; 2nd degree relatives: grandparents, aunts, uncles; 3rd degree relatives: great grandparents or cousins. Figure printed with permission from Can J Gastroenterol 2004;18:93-99. Also see: Colorectal Screening for Cancer Prevention in Asymptomatic Patients, March 2013. Available from http://www.bcguidelines.ca/pdf/colorectal_screening.pdf

Cervical Cancer Screening
• either conventional Papanicolaou (Pap) smear or liquid based cytology testing
• endocervical and exocervical cell sampling (aim is to sample the transitional zone)
• best identifies squamous cell abnormalities, less reliable for glandular abnormalities
  • false positives 5-10%, false negatives 10-40% (for single test)
  • false negative rate 50% for existing cervical cancer
• cervical cancer screening guidelines differ by provincial jurisdiction (see The Society of Obstetricians and Gynaecologists of Canada guidelines)

  Canadian Task Force for Preventative Care Guidelines
• screen all women age ≥25 ≤69 yr (age 25-29: weak recommendation; moderate quality evidence, age 30-69: strong recommendation; high quality evidence)
• women age ≥70: if 3 normal tests in a row and no abnormal tests in last 10 yr, can discontinue screening (weak recommendation; low quality evidence)
• Ontario guidelines
  - screen all women age ≥21 who are or have ever been sexually active (includes intercourse or digital/oral activity with partner of either gender)
  - if cytology is normal, can screen every 3 yr
  - women age ≥70: if 3 successive negative Pap tests in last 10 yr, can discontinue screening
  - women who are not sexually active by age 21 should delay cervical cancer screening until sexually active
• pregnant women and women who have sex with women should follow the routine cervical screening regimen
• women who have had a hysterectomy
  - total: discontinue screening if hysterectomy was for benign disease and no history of cervical dysplasia or HPV infection, continue to swab vaginal vault if history of uterine malignancy/dysplasia
  - subtotal: continue screening according to guidelines
• exceptions to guidelines
  - immunocompromised (transplant, steroids, diethylstilbestrol exposure, HIV)
  - previously unscreened patients
• for more information on cervical cancer (see Gynecology, GY44)

![Cervical Cancer Screening Diagram]

Figure 2. Decision making chart for cervical cancer screening (not applicable for adolescents)
AGUS = atypical glandular cells of unknown significance; ASCUS = abnormal squamous cells of unknown significance; ASC-H = abnormal squamous cells cannot rule out HSIL; LSIL = low grade squamous intraepithelial lesion; TZ = transitional zone
Adapted from: Ontario Cervical Screening Cytology Guidelines. May 2012

Prostate Cancer Screening

• Canadian Task Force for Preventative Care Guidelines
  - screening for prostate cancer with the prostate specific antigen test is not recommended for any age group (age <55: strong recommendation; low quality evidence, age 55-69: weak recommendation; moderate quality evidence, age >70: strong recommendation; low quality evidence)

Prostate Cancer Mortality at 11 Years of Follow-Up
NEJM 2012;366:981-990
Study: Updated “ERSPC” study – multicentre randomized trial of screening for prostate cancer using PSA.
Patients: 162,388 men, ages 55-69 from 8 different European countries.
Intervention: PSA-based screening.
Main Outcome: Mortality from prostate cancer.
Results: After median follow up of 11 yr, the RRR of death from prostate cancer was 21%. The ARR was 1.07 deaths/1,000 men. NNT = 1,055 – therefore to prevent one death from prostate cancer at 11 yr follow up, 1,055 men would need to be screened.
Health Promotion and Counselling

- health promotion is the most effective preventive strategy
- 40-70% of productive life lost annually is preventable
- there are several effective ways to promote healthy behavioural change, such as discussions appropriate to a patient's present stage of change
- for more information about motivational interviewing, see www.motivationalinterviewing.org

Motivational Strategies for Behavioural Change

Table 2. Motivational Strategies for Behavioural Change

<table>
<thead>
<tr>
<th>Patient’s Stage of Change</th>
<th>Physician’s Aim</th>
<th>Physician’s Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Contemplation</td>
<td>Encourage patient to consider the possibility of change</td>
<td>Raise issue in a sensitive manner</td>
</tr>
<tr>
<td></td>
<td>Assess readiness for change</td>
<td>Offer (not impose) a neutral exchange of information to avoid resistance</td>
</tr>
<tr>
<td></td>
<td>Increase patient’s awareness of the problem and its risks</td>
<td></td>
</tr>
<tr>
<td>Contemplation</td>
<td>Understand patient’s ambivalence and encourage change</td>
<td>Offer opportunity to discuss pros and cons of change using reflective listening</td>
</tr>
<tr>
<td></td>
<td>Build confidence and gain commitment to change</td>
<td></td>
</tr>
<tr>
<td>Preparation</td>
<td>Explore options and choose course most appropriate to patient</td>
<td>Offer realistic options for change and opportunity to discuss inevitable difficulties</td>
</tr>
<tr>
<td></td>
<td>Identify high-risk situations and develop strategies to prevent relapse</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Continue to strengthen confidence and commitment</td>
<td></td>
</tr>
<tr>
<td>Action</td>
<td>Help patients design rewards for success</td>
<td>Offer positive reinforcement and explore ways of coping with obstacles</td>
</tr>
<tr>
<td></td>
<td>Develop strategies to prevent relapse</td>
<td>Encourage self-rewards to positively reinforce change</td>
</tr>
<tr>
<td></td>
<td>Support and reinforce convictions towards long-term change</td>
<td></td>
</tr>
<tr>
<td>Maintenance</td>
<td>Help patient maintain motivation</td>
<td>Discuss progress and signs of impending relapse</td>
</tr>
<tr>
<td></td>
<td>Review identified high-risk situations and strategies for preventing relapse</td>
<td></td>
</tr>
<tr>
<td>Relapse</td>
<td>Help patient view relapse as a learning experience</td>
<td>Offer a non-judgmental discussion about circumstances surrounding relapse and how to avoid relapse in the future</td>
</tr>
<tr>
<td></td>
<td>Provide support appropriate to present level of readiness post-relapse</td>
<td>Reassess patient’s readiness to change</td>
</tr>
</tbody>
</table>


Nutrition

General Population
- Canada’s Food Guide is appropriate for individuals age ≥2
- counsel on variety, portion size, and plate layout

Table 3. Canada’s Food Guide 2011 Recommendations for Children >2 and Adults (# of servings/d)

<table>
<thead>
<tr>
<th>Age in Years</th>
<th>Children</th>
<th>Teens</th>
<th>Adults</th>
<th>Choose More From</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-3</td>
<td>4-8</td>
<td>9-13</td>
<td>14-18</td>
<td>19-50</td>
</tr>
<tr>
<td>Grain Products</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>F:6 F:6-7 F:6</td>
</tr>
<tr>
<td>Vegetables and Fruit</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>M:7 M:8 M:7</td>
</tr>
<tr>
<td>Milk and Alternatives</td>
<td>2</td>
<td>2</td>
<td>3-4</td>
<td>F:7 F:7-8 7</td>
</tr>
<tr>
<td>Meat and Alternatives</td>
<td>1</td>
<td>1</td>
<td>1-2</td>
<td>M:8 M:8-10 3</td>
</tr>
</tbody>
</table>

Handy Serving Size Comparisons
- 3 oz meat, fish, poultry → palm of hand
- 1 cup dairy (milk/yogurt) → size of fist
- Bread/grains → one slice, palm of hand
- ½ cup rice/pasta → one hand cupped
- 1 cup of fruit/vegetables → two cupped hands
- 1 oz cheese → full length of thumb
- 1 tsp oil/butter → tip of thumb
- Nuts/chips/snacks → palm covered

Energy Content of Food
- Carbohydrates 4 kcal/g
- Protein 4 kcal/g
- Fat 9 kcal/g
- Ethanol 7 kcal/g

Calculating Total Daily Energy Expenditure (TDEE)
- Roughly 35 kcal/kg/d
- Varies by age, weight, sex, and activity level
- Average 2000-2100 kcal/d for women, 2700-2900 kcal/d for men

Canadian Cancer Society (CCS) Recommendations for Vitamin D Use
- Based on CCS research on Vitamin D and the prevention of colorectal, breast and prostate cancer
- In consultation with their healthcare provider, the Society is recommending that:
  - Adults living in Canada should consider taking Vitamin D supplementation of 1,000 international units (IU) a day during the fall and winter
  - Adults at higher risk of having lower Vitamin D levels should consider taking Vitamin D supplementation of 1,000 IU/d all year round. This includes people: who are older, with dark skin, who do not go outside often, and who wear clothing that covers most of their skin
  - Babies who are exclusively breast-fed: 400 IU/d
Cardiovascular Disease Prevention

Table 4. Dietary Guidelines for Reducing Risk of Cardiovascular Disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat, Carbohydrates, Protein</td>
<td></td>
</tr>
<tr>
<td>Overall fat intake: 25-27% of total energy</td>
<td>Lower LDL</td>
</tr>
<tr>
<td>Saturated fat: 5-6% of total energy</td>
<td></td>
</tr>
<tr>
<td>Trans fat: reduce intake, replace with MUFAs or PUFAs</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates: 55-59% of total energy</td>
<td></td>
</tr>
<tr>
<td>Protein: 15-18% of total energy</td>
<td></td>
</tr>
<tr>
<td>Omega-3 Fatty Acid Rich Foods</td>
<td>Decreased sudden death, death from CAD</td>
</tr>
<tr>
<td>≥2 servings/wk of fish (especially oily fish like salmon)</td>
<td>Lower TG</td>
</tr>
<tr>
<td>Salt</td>
<td>Lower BP</td>
</tr>
<tr>
<td>≤2,400 mg/d</td>
<td>Combining decreased sodium intake with the DASH diet (see below) achieves even greater BP-lowering effects</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Decreased risk of hypertriglyceremia, HTN</td>
</tr>
<tr>
<td>≤3 drinks/d for men, max 15/wk</td>
<td></td>
</tr>
<tr>
<td>≤2 drink/d for women, max 10/wk</td>
<td></td>
</tr>
<tr>
<td>Dietary Approaches</td>
<td></td>
</tr>
<tr>
<td>DASH diet (Dietary Approaches to Stop Hypertension), recommended by the American Heart Association (AHA)</td>
<td>Lower BP, lower LDL</td>
</tr>
<tr>
<td>Diet: high in vegetables/fruits, low-fat dairy, whole grains, poultry, fish, and nuts</td>
<td></td>
</tr>
<tr>
<td>Low in sweets, sugar-sweetened beverages, red meats</td>
<td></td>
</tr>
<tr>
<td>Macronutrients: low in saturated total fat and cholesterol, high in potassium, magnesium, calcium, protein, and fibre</td>
<td></td>
</tr>
</tbody>
</table>

MUFAs = monounsaturated fatty acids; PUFAs = polyunsaturated fatty acids

References

Obesity

- see Canadian Task force on Preventive Health Care recommendations (CMAJ February 2015) at: canadiantaskforce.ca/ctfphc-guidelines/2015-obesity-adults/
- body mass index (BMI) = weight (kg)/height (m)^2 = weight (lbs)/height (in)^2 x 703; BMI is a poor predictor of obesity
- waist circumference (WC) = flexible tape placed on horizontal plane at iliac crest, normal depends on ethnic background
- increased WC for BMI 25-35 increases the risk of cardiovascular disease and type 2 diabetes

Table 5. Classification of Weight by BMI, Waist Circumference, and Associated Disease Risks in Adults

<table>
<thead>
<tr>
<th>BMI (kg/m^2)</th>
<th>Obesity Class</th>
<th>Men ≤102 cm (40 in)</th>
<th>Women ≤88 cm (35 in)</th>
<th>Men &gt;102 cm (40 in)</th>
<th>Women &gt;88 cm (35 in)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>18.5-24.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0-29.9</td>
<td>Increased</td>
<td></td>
<td>High</td>
<td></td>
</tr>
<tr>
<td>Obesity Class I</td>
<td>30.0-34.9</td>
<td></td>
<td></td>
<td>High</td>
<td>Very High</td>
</tr>
<tr>
<td>Obesity Class II</td>
<td>35.0-39.9</td>
<td></td>
<td></td>
<td>Very High</td>
<td>Very High</td>
</tr>
<tr>
<td>Obesity Class III</td>
<td>40.0 +</td>
<td>Extremely High</td>
<td></td>
<td>Extremely High</td>
<td></td>
</tr>
<tr>
<td>(Extreme Obesity)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Epidemiology

- 16% (4 million) of people ≥18 yr old are obese, 32% (8 million) are overweight in Canada, according to StatsCan (2007)
- obesity rate in people of Aboriginal origin is 1.6 times higher than the national average
- proportion of children aged 6-11 who are overweight has more than doubled in the last 25 yr; percentage of overweight adolescents has tripled
- overweight and obesity rates in children are directly proportional to screen time (see Exercise, FM10)
- 10-15% of population consume <30% fat daily
- obese persons generally consume more energy-dense food which tends to be highly processed, micronutrient poor, and high in fats, sugars, or starch

Osteoporosis Canada

Recommendations for Calcium and Vitamin D Daily Requirements
- Vitamin D: 800-1,000 IU for individuals age <50 yr; 800-2,000 IU for individuals ≥50 yr
- Calcium: 1,000 mg daily from all sources for individuals 19-50 yr and pregnant/fatigating women; 1,200 mg daily for individuals ≥50 yr

Effectiveness of behavioral and pharmacologic treatment for overweight and obesity in adults. CMAJ Open 2014;2:E36-17
- Study: Review of 88 RCTs comparing the interventions: diet, exercise, diet and exercise, lifestyle, oralist or metformin to control groups: no intervention, usual care, placebo or minimal interventions (e.g. newsletter or single information session on healthy living).
- Population overweight and obese adults >18 yr.
- Outcome measures: weight 12 mo post intervention and secondary health outcomes: total cholesterol, LDL, fasting blood glucose, incidence of DM-2, systolic and diabetic BP.
- Results:
  1. Intervention participants had a greater mean weight loss, greater reduction in waist circumference and greater reduction in BMI.
  2. For cholesterol and fasting glucose- the reduction was greater for participants in pharmacologic plus behavioral intervention as opposed to those using behavioral interventions alone.
  3. A diagnosis of new onset type 2 DM was less likely to occur in intervention participants compared with the control group.
- Conclusion: Behavioral and pharmaceutical interventions for overweight and obesity in adults leads to clinically significant results.

Losing Weight

- Aim for caloric intake 500-1000 kcal/d less than total daily energy expenditure (TDEE)
- 3500 kcal energy expended/ lb of fat burned
- Results in 1-2 lb (0.5-1 kg) weight loss per wk
- Achieved by combination of increased activity and/or decreased caloric intake

Low BMI Associations

- Osteoporosis
- Eating disorders
- Under-nutrition
- Pregnancy complications

Adverse Medical Consequences of Obesity

- Type 2 DM
- CAD
- Stroke
- HTN
- Gallbladder disease
- Non-alcoholic steatohepatitis
- Complications of pregnancy
- Dyslipidemia
- Osteoarthritis
- Sleep apnea
- Certain cancers
- CHF
- Low back pain
- Increased total mortality
Screening Recommendations
- the CANRISK or FINRISC scores can be used to assess the risk for type 2 diabetes in overweight and obese patients
- BMI risk assessment should be done every 3-5 yr in people at high risk of developing diabetes within 10 yr

Management

Behavioural/Lifestyle
- weight loss of >5% is clinically significant for reducing many cardiovascular risk factors (e.g. elevated blood pressure, glucose and lipids)
- efficacious behavioural interventions were greater than 12 months duration, included diet and/or exercise and/or lifestyle components, and included group and individual sessions
- no intervention for weight gain prevention in individuals BMI 18.5–24.9
- structured behavioural and lifestyle interventions should be offered or arranged for overweight individuals BMI >25
- strong recommendation for those with increased risk of Type 2 DM
- BMI >35 + risk factors or BMI >40 are candidates for bariatric surgery failing behavioural modification

Pharmacologic
- the task force recommends against pharmacologic intervention to manage overweight and obesity, although some patients may prefer medications and be good candidates for pharmacologic treatment
- high benefit of behavioural modification alone, NNH 10 (mostly GI side effects) for pharmacotherapy

### Figure 4. 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children (summary) Adapted from: CMAJ 2007;176:S1-S13

<table>
<thead>
<tr>
<th>Overweight or obese adult</th>
<th>IMPORANT MESSAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measure BMI</td>
<td>A modest weight loss of 5-10% of body weight is beneficial</td>
</tr>
<tr>
<td>Measure waist circumference if BMI is &gt;25 and ≤35 kg/m²</td>
<td>Weight maintenance and prevention of weight regain should be considered as long-term goals</td>
</tr>
</tbody>
</table>

#### Management

**Lifestyle modification program**
- **Nutrition:** Reduce energy intake by 500-1000 kcal/d
- **Physical activity:** Initially 30 min of moderate-intensity 3-5 times/wk; eventually >60 min per wk for 6 mo

**Lifestyle modification program**
- **Assess readiness to change behaviours and barriers to weight loss**
- **Entreat health team to advise lifestyle modification program**

- **Nutrition therapy**
  - **Reduce energy intake by 500-1000 kcal/d**
- **Physical activity**
  - **Initially 30 min of moderate-intensity 3-5 times/wk; eventually >60 min per wk for 6 mo**

### Pharmacotherapy
- **Orlistat:** gastrointestinal lipase inhibitor, reduces fat absorption by 30% by inhibition of pancreatic lipase
- **Orlistat** is associated with several adverse effects and not approved for clinical use longer than 2 yr
- **Orlistat should be avoided in people with inflammatory or chronic bowel disease**

### Hyperlipidaemia Signs
- Atheroma: plaques in blood vessel walls
- Xanthelasmata: a sharply demarcated yellowish deposit of cholesterol underneath the skin, usually on or around the eyelid
- Tendinous xanthoma: lipid deposit in tendon (especially Achilles)
- Eruptive xanthoma: hypertiglyceridaemia induced reddish yellow, pruritic, and painful papular or nodular rash
- Lipemia retinalis: thin atheroma seen in the retinal blood vessels
- Coronel arcus (arcus senilis): lipid deposit in cornea

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**The Latest Evidence on Fad Diets...**

Comparison of the Atkins, Ornish, Weight Watchers, and Zone Diets for Weight Loss and Heart Disease Risk Reduction

**Purpose:** To assess the effectiveness and adherence rates of four popular diets for weight loss and reduction of cardiac risk factors.

**Study Characteristics:** Single centre RCT at academic medical centre in Boston, MA; 160 participants were randomized to either Atkins (carbohydrate restriction), Zone (macronutrient balanced and low glycemic load), Weight Watchers (low calorie/portion size), or Ornish (fat restriction) diet groups for a period of 18 mo.

**Participants:** Adults age 22-72 with known HTN, dyslipidaemia, or fasting hyperglycaemia.

**Results:** Assuming that participants who discontinued the study remained at baseline, the mean weight loss at 1 yr (and self selected dietary adherence rates per self report) were 2.1 kg for Atkins (53% of participants completed, p = 0.009), 3.2 kg for the Zone (65% of participants completed, p = 0.002), 3.0 kg for Weight Watchers (65% completed, p = 0.001), 3.3 kg for Ornish (50% completed, p = 0.007). Each diet significantly reduced the LDL:HD ratio by ~10% (p<0.05), with no significant effects on blood pressure or glucose. Amount of weight loss was associated with adherence level (r = 0.60, p<0.001) but not with diet type (r = 0.07, p=0.40). Weight loss for each diet was significantly associated with reduction in levels of total/HDL cholesterol (r=0.36), C-reactive protein (r=-0.37), and insulin (r=0.39), with no significant difference between diets.

**Conclusion:** Each popular diet was associated with modest weight loss and reduction of several cardiac risk factors. Adherence level, and not diet type, was the most important predictor of weight loss and cardiac risk factor reduction.

---

**IMPORTANT MESSAGE**

- Assess readiness to change behaviours and barriers to weight loss
- Devise goals and lifestyle modification program for weight loss and reduction of risk factors
- Weight loss goal: 5-10% of body weight, or 0.5-1 kg (1-2 lb) per wk for 6 mo
- Health team to advise lifestyle modification program
- Nutrition: Reduce energy intake by 500-1000 kcal/d
- Physical activity: Initially 30 min of moderate intensity 3-5 times/wk; eventually >60 min per wk for 6 mo

**Satisfactory progress or goal achieved?**

- Yes
  - Regular monitoring
    - Assist with weight maintenance
    - Reinforce healthy eating and physical activity advice

- No
  - Weight maintenance and prevention of weight regain
    - Nutrition therapy
    - Physical activity
    - Cognitive behavioural therapy
    - Address other risk factors: periodic monitoring of weight, BMI and waist circumference q1-2yr

  - Pharmacotherapy
    - BMI ≥27 kg/m² + risk factors or BMI ≥30 kg/m²
    - Adjunct to lifestyle modifications: consider if patient has not lost 0.5-1 kg (1-2 lb) per wk by 3-6 mo after lifestyle changes

  - Bariatric surgery
    - BMI ≥35 kg/m² + risk factors or BMI ≥40 kg/m²
    - Consider if other weight loss attempts have failed. Requires lifelong medical monitoring

---

**Figure 4.** 2006 Canadian clinical practice guidelines on the management and prevention of obesity in adults and children (summary) Adapted from: CMAJ 2007;176:S1-S13
Dyslipidemia

- see Endocrinology, E2
- defined as abnormal elevation of plasma cholesterol or triglyceride levels

Assessment
- measure fasting serum TC, LDL-C, HDL-C, and TG
- screen with full fasting lipid profile q1-3yr in males >40 yr and females >50 yr or who are menopausal, or at any age for adults with additional dyslipidemia risk factors (see sidebar)
- screen for secondary causes: hypothyroidism, chronic kidney disease, DM, nephrotic syndrome, liver disease
- risk category
  - estimate using the model for 10 yr CAD risk developed from the Framingham data (Framingham Risk Score – FRS)
  - FRS calculated based on the following factors: gender, age, HDL-C, total cholesterol, sBP, smoking, DM
  - family history of CVD <55 male relative or <65 in female relative doubles FRS
  - to be completed for men age 40-75, and women age 50-75 q3-5yr
  - cardiovascular age calculated as patient’s age ± the difference between his or her estimated remaining life expectancy

- used to increase adherence to therapy and reaffirm positive effect of following therapy
- treatment decisions focus on LDL-C level and/or FRS risk; the alternate primary targets are apolipoprotein B (apo B) and non-HDL-C (not used widely yet)
  - if moderate risk and LDL-C <3.5, treatment decision thresholds shifted to apo B >1.2g/L or non-HDL-C >4.3 mmol/L
  - other targets include: TC:HDL-C ratio, apo B:apo AI ratio, hs-CRP (used more for risk stratification of CAD), non-HDL-C, and serum TG levels

### Table 6. Target Lipid Values for Primary Prevention of CAD (2012 Canadian Cholesterol Guidelines)

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Initiate Treatment if</th>
<th>Primary Targets</th>
<th>Alternate</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (FRS ≥20%)</td>
<td>Consider treatment in all patients</td>
<td>LDL-C ≤2 mmol/L or ≥50% decrease in LDL-C</td>
<td>apo B &lt;0.80 g/L or non-HDL-C ≤2.6 mmol/L</td>
</tr>
<tr>
<td>Also: AAA, history of DM (&gt;40 yrs, DM for 15 yr and age &gt;30, microvascular complications), CAD, PVD, atherosclerosis, CKD, or Male with HTN plus one of: smoking, EKG abnormality, LVH, Fam hx of premature death, age &gt;55 yr, TC/ HDL-C &gt;6, microalbuminuria</td>
<td>LDL-C ≥3.5 mmol/L</td>
<td>≤2 mmol/L or ≥50% decrease in LDL-C</td>
<td>apo B &lt;0.80 g/L or non-HDL-C ≤2.6 mmol/L</td>
</tr>
<tr>
<td>Moderate (FRS 10-19%)</td>
<td>For LDL-C &lt;3.5 consider if: apo B ≥1.2 g/L or non-HDL-C ≥4.3 mmol/L</td>
<td>LDL-C ≥5.0 mmol/L</td>
<td>Familial hypercholesterolemia</td>
</tr>
</tbody>
</table>

Management
- intensity and type of treatment is guided by “risk category” assigned (see Table 6)

1. health behaviours (can decrease LDL-C by up to 10%)
   - smoking cessation: probably the most important for preventing CAD
   - dietary modification: reduce saturated fat, red meat, refined sugar, alcohol; consume nuts, fruits/vegetables, poultry, fish
   - physical activity: at least 150 min of moderate to vigorous intensity aerobic exercise per wk
   - employ consistent lifestyle modifications for at least 3 mo before considering drug therapy; high risk patients should start treatment immediately with concurrent health behaviour interventions

2. pharmacologic therapy (can decrease LDL-C by up to 40%)
   - for a comparison of dyslipidemia medications, see Endocrinology, E53
   - 1st line monotherapy: statins (HMG-CoA reductase inhibitors)
     - risks: myopathy and hepatotoxicity
     - if severe side effects: ezetimibe (cholesterol absorption inhibitor) can be used for 19% reduction in LDL-C
   - post-ACS, cholesterol absorption inhibitors (e.g. ezetimibe) in addition to simvastatin reduced mortality, attained lipid targets <1.8, and improved outcomes in high risk individuals
   - lower evidence for other agents: bile acid sequestrants, nicotinic acid, fibrates, psyllium

Non-fasting Lipids vs. Fasting Lipids
- Non-fasting (TC and non-HDL cholesterol) can be used for Framingham Risk Assessment and hold same prognostic value as fasting lipids
- In fasted vs. non-fasted samples, Non-HDL and TC varies by 2%, LDL-C by 10% and TG by 20%
- Recently, non-fasting LDL-C has the same prognostic value as fasting LDL-C

Safety of Statins: An Update
- Therapeutic Advances in Drug Safety 2012;3:133-144
- Trials have shown that statin therapy slightly increases the incidence of diabetes; however, the absolute risk is small. Relative to the reduction in coronary events, the clinical significance is not great enough to recommend against their use.
monitoring
- ALT, CK, Cr at baseline then 6 wk later for signs of transaminitis or myositis; tolerate rise in CK up to 10 times upper limit of normal vs. 2-3 times if symptomatic, or serum creatinine rise of ≤ 25%;
- no routine repeated measures of ALT and creatine kinase necessary in asymptomatic patients using statin therapy
- if adequate response is achieved, evaluate fasting lipids q6-12mo

Isolated Hypertriglyceridemia
- does not increase your cardiovascular risk
- normal HDL-C and TC, elevated TG
- mild ≥2.2 mmol/L (≥ 200 mg/dL); marked ≥5.6 mmol/L (≥500 mg/dL)
- principal therapy is lifestyle modification
  - weight loss, exercise, avoidance of smoking and alcohol, effective blood glucose control in diabetics, increased omega-3 fatty acid intake
  - severe hypertriglyceridemia (typically >10 mmol/L) is associated with an increased risk of acute pancreatitis
- drug therapy (used to prevent pancreatitis, NOT cardiovascular disease!)
  - nicotinic acid
  - fibrates

Exercise

Epidemiology
- 25% of the population exercises regularly, 50% occasionally, 25% are sedentary

Management
- assess current level of fitness, motivation, and access to exercise
- encourage warm up and cool down periods to allow transition between rest and activity and to avoid injuries
- exercise with caution for patients with CAD, DM (risk of hypoglycemia), exercise-induced asthma
- patients with known CAD should have cardiac assessment prior to commencing exercise
- benefits of exercise
  - reduces risk of premature death, heart disease, stroke, HTN, certain types of cancer, type 2 DM, osteoporosis, and overweight/obesity
  - leads to improved fitness, strength, and mental health (morale and self-esteem)

Table 7. Canadian Physical Activity and Sedentary Behaviour Guidelines (2012 CSEP Guidelines)

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Physical Activity Guidelines</th>
<th>Example Activities</th>
<th>Sedentary Behaviour Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant (&lt;1y)</td>
<td>Active several times daily</td>
<td>Interactive floor-based play including tummy time, reaching for toys, crawling</td>
<td>Minimize time spent sedentary, including sitting and being restrained (stroller, etc.) Screen time not recommended</td>
</tr>
<tr>
<td>Toddler (1-2)</td>
<td>Accumulate 180 min of physical activity at any intensity spread throughout the day</td>
<td>Moving around the home Climbing stairs Exploring environment Brisk walking, running Dancing</td>
<td>apo B &lt;0.80 g/L non HDL-C ≤2.6mmol/L</td>
</tr>
<tr>
<td>Preschool (2-4)</td>
<td>Accumulate 60 min of moderate to vigorous intensity physical activity daily</td>
<td>Moderate: bike riding, playground Vigorous: running, swimming</td>
<td>Minimize time spent being sedentary Limited recreational screen time no more than 2 h per day Limit sedentary (motorized) transport, sitting, and time spent indoors</td>
</tr>
<tr>
<td>Children (5-11)</td>
<td>Accumulate 60 min of moderate to vigorous intensity physical activity daily</td>
<td>Moderate: skating, bike riding Vigorous: running, roller blading</td>
<td></td>
</tr>
<tr>
<td>Youth (12-17)</td>
<td>Accumulate 60 min of moderate to vigorous intensity physical activity daily Vigorous intensity activities at least 3 d per wk Activities that strengthen muscle and bone at least 3 d per wk</td>
<td>Moderate: skating, bike riding Vigorous: running, roller blading</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Definition of Metabolic Syndrome
- Central obesity
  - Men – waist circumference ≥94 cm
  - Women – waist circumference ≥80 cm
- Plus any TWO of the following four factors

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>TG level</td>
<td>≥1.7 mmol/L (150 mg/dL)</td>
</tr>
<tr>
<td>HDL-C level</td>
<td>Men &lt;1.0 mmol/L (40 mg/dL) Women &lt;1.3 mmol/L (50 mg/dL)</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>≥130/85 mmHg</td>
</tr>
<tr>
<td>Fasting glucose level</td>
<td>≥5.6 mmol/L (100 mg/dL)</td>
</tr>
</tbody>
</table>
**Table 7. Canadian Physical Activity and Sedentary Behaviour Guidelines (2012 CSEP Guidelines) (continued)**

<table>
<thead>
<tr>
<th>Age Category</th>
<th>Physical Activity Guidelines</th>
<th>Example Activities</th>
<th>Sedentary Behaviour Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adults (18-64)</td>
<td>Accumulate 150 min of moderate to vigorous intensity aerobic physical activity per wk, in bouts of 10 m or more. It is beneficial to add muscle and bone strengthening activities using major muscle groups, at least 2 d per wk.</td>
<td>Moderate: brisk walking, bike riding&lt;br&gt;Vigorous: jogging, cross country skiing</td>
<td>No specific guidelines</td>
</tr>
<tr>
<td>Older Adults (65 and older)</td>
<td>Moderate: brisk walking, bike riding&lt;br&gt;Vigorous: cross country skiing&lt;br&gt;Swimming&lt;br&gt;Those with poor mobility should perform physical activities to enhance balance and prevent falls</td>
<td>No specific guidelines</td>
<td></td>
</tr>
</tbody>
</table>

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**Smoking Cessation**

**Epidemiology**
- smoking is the single most preventable cause of premature illness and death
- 70% of smokers see a physician each year
- 2012 Canadian data from the Canadian Tobacco Use Monitoring Survey (CTUMS) on population age ≥15
  - 16% are current smokers (lowest since 1965)
  - highest prevalence in age group 20-24 (20%)
  - 11% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing

**Management**
- general approach
  - identify tobacco users; elicit smoking habits, previous quit attempts and results
  - CAN-ADAPPT 2012 guidelines
    - tobacco use status should be updated for all patients regularly (Grade 1A)
    - health care providers should clearly advise patients to quit (Grade 1C)
    - health care providers should also monitor the patients’ mental health status/other addictions while quitting smoking. Medication dosage should be monitored and adjusted as necessary (Grade 1A)
- every smoker should be offered treatment
  - combining counselling and smoking cessation medication is more effective than either alone (Grade 1A)
  - make patient aware of withdrawal symptoms
    - low mood, insomnia, irritability, anxiety, difficulty concentrating, restlessness, decreased heart rate, increased appetite
    - ≥4 counselling sessions >10 min each with 6-12 mo follow-up yields better results
  - ≥14 abstinent with counselling vs. 10% without counselling
  - approach depends on patient’s stage of change (see *Motivational Strategies for Behavioural Change*, FM6)
- willing to quit
  - provision of social support, community resources (self-help, group, helpline, web-based strategies)
  - pregnant patients: counselling is recommended as 1st line treatment (Grade 1A). Nicotine replacement therapy (NRT) should be made available to pregnant women who are unable to quit using non-pharmacologic methods; intermittent NRT use (lozenges, gum) is preferred over continuous dosing of the patch (Grade 1C). Use bupropion (no evidence of fetal or reproductive harm) only if benefits > risks; consult Motherisk. Varenicline has not been studied in pregnancy and should not be used in pregnant women
- pharmacologic therapy
  1. Nicotine Replacement Therapy (NRT)
    - 19.7% abstinent at 12 mo with NRT vs. 11.5% for placebo
    - no difference in achieving abstinence for different forms of NRT
    - reduces cravings and withdrawal symptoms without other harmful substances that are contained in cigarettes
    - use with caution: immediately post-MI, serious/worsening angina, serious arrhythmia
    - advise NO smoking while using NRT
  2. Antidepressants (note: mode of action appears to be independent of antidepressant effect)
    - Bupropion SR (Zyban®)
      - 21% abstinent at 12 mo vs. 8% for placebo
      - no advantage for NRT vs. bupropion (similarly effective)
    - Varenicline
      - 11% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing
      - highest prevalence in age group 20-24 (20%)
      - 16% are current smokers (lowest since 1965)
      - 11% of youth age 15-19 smoke (decreased from 25% in 2000): more males smoke than females; number of cigarettes consumed per day also decreasing
  - in ≥15 years of age
    - accumulate 150 min of moderate to vigorous intensity aerobic physical activity per wk, in bouts of 10 m or more. It is beneficial to add muscle and bone strengthening activities using major muscle groups, at least 2 d per wk.
  - low body mass index (BMI) (≥15 years of age) adults should be encouraged to increase their physical activity and bone strengthening activities using major muscle groups, at least 2 d per wk.
  - Those with poor mobility should perform physical activities to enhance balance and prevent falls

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**The 5 A’s for Patients Willing to Quit**
- Ask, if the patient smokes
- Advise patients to quit
- Assess willingness to quit
- Assist in quit attempt
- Arrange follow-up

**The 2-3 Pattern of Smoking Cessation**
- Onset of withdrawal is 2-3 h after last cigarette
- Peak withdrawal is at 2-3 d
- Expect improvement of withdrawal symptoms at 2-3 wk
- resolution of withdrawal at 2-3 mo
- Highest relapse rate at 2-3 mo

**Assist Patient in Developing Quit Plan**
- STAR
  - Set quit date
  - Tell family and friends (for support)
  - Anticipate challenges (e.g. withdrawal)
  - Remove tobacco-related products (e.g. ashtrays/lighters)

**Antidepressants for Smoking Cessation**
- This systematic review of 90 randomized trials compared antidepressant medication to placebo or alternative pharmacotherapy for smoking cessation and where follow-up was longer than 6 mo.
- Conclusions: The antidepressants bupropion and nortriptyline can aid smoking cessation and have a similar efficacy to NRT. Bupropion is less effective than varenicline. Neither SSRIs (e.g. fluoxetine) nor MAOIs aid smoking cessation.
3. Varenicline (Champix®)
- partial nicotinic receptor agonist (to reduce cravings) and partial competitive nicotinic receptor antagonist (to reduce the response to smoked nicotine)
- more effective than bupropion (23% abstinent from 9–52 wk with varenicline vs. 16% for bupropion vs. 9% with placebo)
- significant side effects may lower patient compliance.

Table 8. Types of Nicotine Replacement Therapy

<table>
<thead>
<tr>
<th>Type</th>
<th>Dosage</th>
<th>Comment</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine Gum (OTC)</td>
<td>2 mg if &lt;25 cig/d</td>
<td>Chew until &quot;peppery&quot; taste then &quot;park&quot;</td>
<td>Mouth soreness</td>
</tr>
<tr>
<td></td>
<td>4 mg if &gt;25 cig/d</td>
<td>between gum and cheek to facilitate</td>
<td>Hiccups</td>
</tr>
<tr>
<td></td>
<td>1 piece q1-2h for 1-3 mo</td>
<td>Continue to chew-park intermittently</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>(max 24 pieces/d)</td>
<td>for 30 min</td>
<td>Jaw ache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Most are transient</td>
</tr>
<tr>
<td>Nicotine Patch (OTC)</td>
<td>Use for 8 wk</td>
<td>Start with lower dose if &lt;10 cig/d</td>
<td>Skin irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Change patch q24h and alternate sides</td>
<td>Insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Palpitations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td>Nicotine Inhaler (OTC)</td>
<td>6-16 cartridges/d for up to 12 wk</td>
<td>Nicotine inhaled through mouth, absorbed in mouth and throat not in lungs</td>
<td>Local irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Coughing</td>
</tr>
<tr>
<td>Nicotine Nasal Spray</td>
<td>Older form of NRT</td>
<td></td>
<td>Local irritation</td>
</tr>
<tr>
<td>(Rx)</td>
<td></td>
<td></td>
<td>coughing</td>
</tr>
</tbody>
</table>

Table 9. Pharmacologic Treatments for Smoking Cessation

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Doseage</th>
<th>Prescribing*</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Inhibits re-uptake of dopamine and/or norepinephrine</td>
<td>150 mg qAM x 3 d</td>
<td>1. Decide on a quit date</td>
<td>Seizure disorder</td>
</tr>
<tr>
<td></td>
<td>Side effects: insomnia, dry mouth</td>
<td>2. Then 150 mg bid x 7-12 wk</td>
<td>2. Continue to smoke for first 1-2 wk of treatment and then completely stop (therapeutic levels reached in 1 wk)</td>
<td>Eating disorder</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. For maintenance consider</td>
<td></td>
<td>MAOI use in past 14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>150 mg bid for up to 6 mo</td>
<td></td>
<td>Simultaneous use of bupropion (Wellbutrin®) for depression</td>
</tr>
<tr>
<td>Varenicline</td>
<td>Partial nicotinic receptor agonist, and partial nicotinic receptor competitive antagonist</td>
<td>1. 0.5 mg qAM x 3 d</td>
<td>1. Decide on a quit date</td>
<td>Caution with pre-existing psychiatric condition</td>
</tr>
<tr>
<td></td>
<td>• Side effects: N/V, constipation, headache, dream disorder, insomnia, increased risk of psychosis, depression, suicidal ideation</td>
<td>2. Then 0.5 mg bid x 4 d</td>
<td>2. Continue to smoke for first wk of treatment and then completely stop</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Continue 1 mg bid x 12 wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>± additional 12 wk as maintenance</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Bupropion and Varenicline may be used in combination with nicotine replacement therapy

- unwilling to quit
  - motivational intervention (5 Rs)
  1. Relevance to patient
    - relevant to patient’s disease status or risk, family or social situation (e.g. having children in the home), health concerns, age, gender
  2. Risks of smoking
    - short-term: SOB, asthma exacerbation, impotence, infertility, pregnancy complications, heartburn, URTI
    - long-term: MI, stroke, COPD, lung CA, other cancers
    - environmental: higher risk in spouse/children for lung CA, SIDS, asthma, respiratory infections
  3. Rewards: benefits
    - improved health, save money, food tastes better, good example to children
  4. Roadblocks: obstacles
    - fear of withdrawal, weight gain, failure, lack of support
  5. Repetition
    - reassure unsuccessful patients that most people try many times before successfully quitting (average number of attempts before success is 7)
- recent quitter
  - highest relapse rate within 3 mo of quitting
  - minimal practice: congratulate on success, encourage ongoing abstinence, review benefits and problems
  - prescriptive interventions: address problem of weight gain, negative mood, withdrawal, lack of support

**Conclusions:** Cytisine increases the chances of successful long-term smoking cessation between two- and threefold compared with pharmacologically unassisted quit attempts. Lower dose regimens also conferred benefits for cessation, while reducing the incidence of adverse events. More participants quit successfully with varenicline than with bupropion.
Alcohol

• see Psychiatry, PS24

Definition
• diagnostic categories occur along a continuum

Epidemiology
• 10-15% of patients in family practice are problem drinkers
• 20-50% of hospital admissions, 10% of premature deaths, 30% of suicides, and 50% of fatal traffic accidents in Canada are alcohol-related
• more likely to miss diagnosis in women or elderly, patients with high socioeconomic status

Assessment
• screen for alcohol dependence with CAGE questionnaire
  ▪ if CAGE positive, explore with further questions for alcohol abuse/dependence
  ▪ assess drinking profile
    ▪ setting, time, place, occasion, with whom
    ▪ impact on: family, work, social
    ▪ quantity-frequency history
      ▪ how many drinks per day?
      ▪ how many days per week?
      ▪ maximum number of drinks on any one day in the past month?
  ▪ if identified positive for alcohol problem
    ▪ screen for other drug use
    ▪ identify medical/psychiatric complications
    ▪ ask about drinking and driving
    ▪ ask about past recovery attempts and current readiness for change

Investigations
• GGT and MCV for baseline and follow-up monitoring
• AST, ALT (usually AST:ALT approaches 2:1 in an alcoholic)
• CBC (anemia, thrombocytopenia), INR (decreased clotting factor production by liver)

Management
• intervention should be consistent with patient’s motivation for change
• individualized counselling and regular follow-up is crucial
• 10% of patients in alcohol withdrawal will have seizures or delirium tremens
• Alcoholics Anonymous/12-steps program
• outpatient/day programs for those with chronic, resistant problems
• family treatment (Al-Anon, Alateen, screen for spouse/child abuse)
• in-patient program if
  ▪ dangerous or highly unstable home environment
  ▪ severe medical/psychiatric problem
  ▪ addiction to drug that may require in-patient detoxification
  ▪ refractory to other treatment programs
• pharmacologic
  ▪ diazepam for withdrawal
  ▪ disulfiram (Antabuse®): impairs metabolism of alcohol by blocking conversion of acetaldehyde to acetic acid, leading to flushing, headache, N/V, hypotension if alcohol is ingested (available in U.S., but no longer available in Canada)
  ▪ naltrexone: competitive opioid antagonist that reduces cravings and pleasurable effects of drinking
  ▪ may trigger withdrawal in opioid-dependent patients
  ▪ acamprosate: glutamate receptor modulator that also reduces craving
• see Psychiatry, PS25

Prognosis
• relapse is common and should not be viewed as failure
• monitor regularly for signs of relapse
• 25-30% of abusers exhibit spontaneous improvement over 1 yr
• 60-70% of individuals with jobs and families have an improved quality of life 1 yr post-treatment

Standard Drink Equivalents
One standard drink = 14 g of pure alcohol
• Beer (5% alcohol) = 12 oz
• Wine (12-17% alcohol) = 5 oz
• Fortified wine = 3 oz
• Hard liquor (40%) = 1.5 oz

CAGE Questionnaire
C Have you ever felt the need to CUT down on your drinking?
A Have you ever felt ANNOYED at criticism of your drinking?
G Have you ever felt GUILTY about your drinking?
E Have you ever had a drink first thing in the morning to steady your nerves or get rid of a hangover? (EYE OPENER)
≥2 for men or ≥1 for women suggests possibility of problem drinking (sensitivity 85%, specificity 89%)

Some Adverse Medical Consequences of Problem Drinking
• GI: gastritis, dyspepsia, pancreatitis, liver disease, bleeds, diarrhea, oral/esophageal cancer
• Cardiac: HTN, alcoholic cardiomyopathy
• Neurologic: Wernicke-Korsakoff syndrome, peripheral neuropathy
• Hematologic: anemia, coagulopathies
• Other: trauma, insomnia, family violence, anxiety/depression, social/family dysfunction, sexual dysfunction, fetal damage

Abstinence
Low Risk Drinking
• <2 drinks/d
• <10 drinks/wk for women
• <15 drinks/wk for men
At Risk Drinking
• Consumption above low-risk level but no alcohol-related physical or social problems
Alcohol Use Disorder
• Physical or social problems
• Continued use despite consequences
• Inability to fulfill life roles
• Legal problems
• No evidence of dependence
• Alcohol Use Disorder

Figure 5. Continuum of alcohol use
Common Presenting Problems

Abdominal Pain

- see Gastroenterology, G4 and General Surgery, GS4

Epidemiology
- 20% of individuals have experienced abdominal pain within the last 6-12 mo
- 90% resolve in 2-3 wk
- only 10% are referred to specialists, of those <10% admitted to hospital

Etiology
- most common diagnosis in family medicine at 28% is “nonspecific abdominal pain,” which has no identifiable cause and is usually self-limited
- GI disorders (e.g. PUD, pancreatitis, IBD, appendicitis, gastroenteritis, IBS, diverticular disease, biliary tract disease)
- urinary tract disorders (e.g. UTI, renal calculi)
- gynecological disorders (e.g. PID, ectopic pregnancy, endometriosis)
- cardiovascular disorders (e.g. CAD, AAA, ischemic bowel)
- other: DKA, porphyria, hypercalcemia, medications (e.g. NSAIDs), alcohol, toxic ingestion, foreign body, psychogenic

Pathophysiology
- type of pain
  - somatic pain: sharp, localized pain
  - visceral pain: dull, generalized pain
- location of pain
  - epigastric (foregut): distal esophagus, stomach, proximal duodenum, biliary tree, pancreas, liver
  - RUQ: biliary, hepatic, colonic, pulmonary, renal
  - LUQ: cardiac, gastric, pancreatic, renal, vascular
  - periumbilical (midgut): distal duodenum to proximal 2/3 of transverse colon,
  - hypogastric (hindgut): distal 1/3 of transverse colon to rectosigmoid region,
  - RLQ: colonic, appendix, gynecologic, renal
  - LLQ: colonic, gynecologic, renal
  - any location: aneurysm, dissection, ischemia, zoster, muscle strain, hernia, bowel obstruction, ischemia, peritonitis, porphyria, DKA

Investigations
- guided by findings on history and physical
- possible blood work: CBC, electrolytes, BUN, Cr, amylase, lipase, AST, ALT, ALP, bilirubin, glucose, INR/PTT, tox screen, β-hCG
- imaging
  - CXR (for free air under the diaphragm) in setting of perforation in surgical abdomen
  - abdominal x-ray, KUB (consider: gas pattern, free air, kidney stones, constipation)
  - ultrasound (renal stones, gallbladder disease, gynecological problems, liver disease, pancreatitis, diverticular disease, appendicitis)
  - CT scan (AAA, appendicitis), non-contrast helical CT-Scan (first choice for renal stones)
- other tests
  - urinalysis
  - endoscopy (for peptic ulcers, gastritis, tumours, etc.)
  - H. pylori testing (urea breath test, serology, biopsy)

Allergic Rhinitis

- see Otolaryngology, OT24

Definition
- inflammation of the nasal mucosa that is triggered by an allergic reaction

Classification
- seasonal
  - symptoms during a specific time of the year
  - common allergens: trees, grass and weed pollens, airborne moulds
- perennial
  - symptoms throughout the year with variation in severity
  - common allergens: dust mites, animal dander, moulds
- persistent allergic rhinitis may lead to chronic rhinosinusitis

Differential Diagnosis
- Acute viral infection
- Vasomotor rhinitis
- Deviated septum
- Nasal polyps
- Acute/chronic sinusitis
- Drug-induced rhinitis
Etiology
• increased IgE levels to certain allergens → excessive degranulation of mast cells → release of inflammatory mediators (e.g. histamine) and cytokines → local inflammatory reaction

Epidemiology
• affects approximately 40% of children and 20-30% of adults
• prevalence has increased in developed countries, particularly in the past two decades
• associated with asthma, eczema, sinusitis, and otitis media

Assessment
• identify allergens
• take an environmental/occupational history
• ask about related conditions (e.g. atopic dermatitis, asthma, sinusitis, and family history)

Management
• conservative
  ▪ minimize exposure to allergens
  ▪ most important aspect of management, often sufficient (may take months)
  ▪ maintain hygiene, saline nasal rinses
• pharmacologic agents
  ▪ oral antihistamines – first line therapy for mild symptoms
    ▪ e.g. cetirizine (Reactine®), fexofenadine (Allegra®), loratadine (Claritin®)
  ▪ intranasal corticosteroids for moderate/severe or persistent symptoms (>1 mo of consistent use to see results)
  ▪ intranasal decongestants (use must be limited to <5 d to avoid rhinitis medicamentosa)
• allergy skin testing
  ▪ for patients with chronic rhinitis
  ▪ symptoms not controlled by allergen avoidance, pharmacological therapy
  ▪ may identify allergens to include in immunotherapy treatment
• immunotherapy (allergy shots)
  ▪ reserved for severe cases unresponsive to pharmacologic agents
  ▪ consists of periodic (usually weekly) subcutaneous injections of custom prepared solutions of one or more antigens to which the patient is allergic

Amenorrhea
• see Gynecology, G10

Anxiety
• see Psychiatry, PS14

Epidemiology
• 25-30% of patients in primary care settings have psychiatric disorders
• many are undiagnosed or untreated; hence the need for good screening
• high rate of coexistence of anxiety disorders and depression

Screening
• screening tools such as the GAD-7 tool
• screening questions
  ▪ Do you tend to be an anxious or nervous person?
  ▪ Have you felt unusually worried about things recently?
  ▪ Has this worrying affected your life? How?

Assessment
• associated symptoms
• risk factors
  ▪ family history of anxiety or depression, past history of anxiety, stressful life event, social isolation, female, comorbid psychiatric diagnosis (e.g. depression)
• assess substance abuse, comorbid depression, stressful life events, trauma, suicidal ideation/self-harm
• to differentiate anxiety disorders, consider symptoms (panic attacks, specific situations/stressors, excessive worry about common concerns, repetitive thoughts and/or behaviours to neutralize the anxiety) and their duration
• Generalized Anxiety Disorder 7-item (GAD – 7) scale to assess level of anxiety

Rhinitis Medicamentosa
Rebound nasal congestion. Occurs with prolonged use (>5-7 d) of vasoconstrictive intranasal medications. Patient may become dependent, requiring more frequent dosing to achieve the same decongestant effect

Symptoms of GAD
AND I C REST
Anxious, nervous, or worried
No control over the worry
Duration >6 mo
Irritability
Concentration impairment
Restlessness
Energy decreased
Sleep impairment
Tension in muscles
Can Fam Physician 2005;51:1340-1342

Differential Diagnosis of Anxiety Disorders
• Panic disorder
• GAD
• Social Anxiety Disorder (previously Social Phobia)
• Agoraphobia
• Specific phobia
• Selective Mutism
• Separation Anxiety Disorder
• Other: GMC, AMC, mood disorder, psychotic disorder, OCD, PTSD
Asthma/COPD

Definition
- asthma
  - chronic but reversible airway inflammation characterized by periodic attacks of wheezing, SOB, chest tightness, and coughing
  - airways hyper-responsive to triggers/antigens leading to acute obstructive symptoms by bronchoconstriction, mucous plugs and increased inflammation
  - cannot be diagnosed at first presentation; called reactive airway disease until recurrent presentations
  - pulmonary function tests (PFTs) can be done from age 6 or when child able to follow instructions to do PFTs
  - peak flow meters are useful in the office and at home for monitoring
- chronic obstructive pulmonary disease (COPD)
  - a group of chronic, progressive, obstructive lung diseases characterized by limited airflow with variable degrees of air sac enlargement and lung tissue destruction
  - emphysema and chronic bronchitis are the most common forms of COPD

Management
- patient education: emphasize prevalence, good recovery rate of anxiety conditions
- lifestyle advice: decrease caffeine and alcohol intake, exercise, relaxation techniques, mindfulness strategies
- self-help materials, community resources (e.g. support groups)
- CBT: cognitive interventions, exposure therapy, etc.
- treat any underlying medical and/or comorbid conditions
- provide support to family and caregivers
- for pharmacotherapy, see Psychiatry, PS47

Rule Out
- Cardiac (post MI, arrhythmia)
- Endocrine (hyperthyroidism, diabetes, pheochromocytoma)
- Respiratory (asthma, COPD)
- Somatoform disorders
- Psychotic disorders
- Mood disorders (depression, bipolar)
- Personality disorder (ODPD)
- Drugs (amphetamines, thyroid preparations, caffeine, OTC for colds/decongestants, alcohol/benzodiazepine withdrawal)

Figure 6. Differentiating anxiety disorders

Figure 7. Expiratory flow volume curves (obstructive, normal, and restrictive disease)
Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. With permission from Elsevier. ©2008

Signs of Poorly Controlled Asthma
- β2 agonist use >4x/wk
- Asthma-related absence from work/school
- Exercise induced asthma
- Night-time symptoms >1x/wk
**Benign Prostatic Hyperplasia**

- see Urology, U7

**Definition**
- hyperplasia of the stroma and epithelium in the periurethral transition zone

**History and Physical**
- include current/past health, surgeries, trauma, current and OTC meds
- specific urinary symptoms
- physical exam must include DRE for size, symmetry, nodularity, and texture of prostate (prostate is symmetrically enlarged, smooth, and rubbery in BPH)

**Investigations**
- urinalysis to exclude UTI and for microscopic hematuria (common sign)
- serum PSA: protein produced by prostatic tissue
  - values
    - <4.0 ng/mL: normal, but must take into account patient’s age and velocity of PSA increase
    - 4-10 ng/mL: consider measuring free/total PSA
    - >10 ng/mL: high likelihood of prostate pathology
- PSA testing is inappropriate in men with a life expectancy less than 10 yr or patients with prostatitis, UTI

**Table 10. Differentiating COPD from Asthma**

<table>
<thead>
<tr>
<th>COPD</th>
<th>Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age of Onset</strong></td>
<td>Usually in 6th decade</td>
</tr>
<tr>
<td></td>
<td>Any age (but 50% of cases diagnosed in children age &lt; 10)</td>
</tr>
<tr>
<td><strong>Role of Smoking</strong></td>
<td>&gt; 10 pack yr</td>
</tr>
<tr>
<td></td>
<td>Not causal, known trigger</td>
</tr>
<tr>
<td><strong>Reversibility of Airflow Obstruction</strong></td>
<td>Airflow obstruction is chronic and persistent</td>
</tr>
<tr>
<td></td>
<td>Airflow obstruction is episodic and usually reversible with therapy</td>
</tr>
<tr>
<td><strong>Evolution</strong></td>
<td>Slow, progressive worsening (with periodic exacerbations)</td>
</tr>
<tr>
<td></td>
<td>Stable, episodic, less than 50% will outgrow</td>
</tr>
<tr>
<td><strong>History of Allergy</strong></td>
<td>Infrequent</td>
</tr>
<tr>
<td></td>
<td>Over 50% patients</td>
</tr>
<tr>
<td><strong>Precipitators</strong></td>
<td>Environmental irritants (air pollution), cigarette smoking, α1-antitrypsin deficiency, viral infection, occupational exposure (firefighters, dusty jobs)</td>
</tr>
<tr>
<td></td>
<td>Environmental irritants (dust, pollen), animal fur, cold air, exercise, URTIs, cigarette smoke, use of β-blockers/ASA</td>
</tr>
<tr>
<td><strong>Symptoms/Signs</strong></td>
<td>Chronic cough, sputum, and/or dyspnea</td>
</tr>
<tr>
<td></td>
<td>Wheeze (hallmark symptom), dyspnea, chest tightness, cough which is worse in cold, at night, and in early AM, prolonged expiration</td>
</tr>
<tr>
<td><strong>Diffusion Capacity</strong></td>
<td>Decreased (more so in pure emphysema)</td>
</tr>
<tr>
<td></td>
<td>Normal (for pure asthma)</td>
</tr>
<tr>
<td><strong>Hypoxemia</strong></td>
<td>Chronic in advanced stages</td>
</tr>
<tr>
<td></td>
<td>Not usually present</td>
</tr>
<tr>
<td><strong>Spirometry</strong></td>
<td>May have improvement with bronchodilators but not universally seen</td>
</tr>
<tr>
<td></td>
<td>Marked improvement with bronchodilators or steroids</td>
</tr>
<tr>
<td><strong>Chest X-Ray</strong></td>
<td>Often normal</td>
</tr>
<tr>
<td></td>
<td>Increased bronchial markings (chronic bronchitis) and chronic hyperinflation (emphysema) often co-exist, bullae</td>
</tr>
<tr>
<td></td>
<td>Often normal or episodic hyperinflation</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td><strong>Mild</strong></td>
</tr>
<tr>
<td></td>
<td>Ongoing patient education, and environmental control</td>
</tr>
<tr>
<td></td>
<td>SABA taken prn as rescue medication + maintenance meds</td>
</tr>
<tr>
<td></td>
<td>Maintenance medications</td>
</tr>
<tr>
<td></td>
<td>Step 1: SABA prn (salbutamol)</td>
</tr>
<tr>
<td></td>
<td>Step 2: SABA prn + LAAC (i.e. tiotropium) or + LABA (e.g. salmeterol)</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Step 3: SABA prn + LAAC + low-dose combined ICS/LABA; consider inhaled vs. oral steroids</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>Step 4: 1 theophylline</td>
</tr>
<tr>
<td></td>
<td>Pneumococcal vaccination, annual influenza immunization</td>
</tr>
<tr>
<td></td>
<td>Ongoing patient education, and environmental control</td>
</tr>
<tr>
<td></td>
<td>SABA taken prn as rescue medication + maintenance meds</td>
</tr>
<tr>
<td></td>
<td>Maintenance medications</td>
</tr>
<tr>
<td></td>
<td>Step 1: Low-dose ICS</td>
</tr>
<tr>
<td></td>
<td>Step 2: Medium/high-dose ICS or low-dose ICS plus either LABA, LT modifier, or long-acting theophylline</td>
</tr>
<tr>
<td></td>
<td>Step 3: Medium/high-dose ICS plus either LABA, LT modifier, or long-acting theophylline</td>
</tr>
<tr>
<td></td>
<td>As above plus immunotherapy ± oral glucocorticosteroids + pneumococcal vaccination, annual influenza immunization</td>
</tr>
</tbody>
</table>

ICS = inhaled corticosteroids; LAAC = long-acting anticholinergic; LABA = long-acting β-agonist; LT modifier = leukotriene modifier; SABA = short-acting β-agonist

---

**What Colour is Your Inhaler?**

<table>
<thead>
<tr>
<th>Name</th>
<th>Body/ Cap Colour</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-Agonists</td>
<td></td>
</tr>
<tr>
<td>Salbutamol – Ventolin®</td>
<td>light blue/teal</td>
</tr>
<tr>
<td>Salmeterol – Serrent®</td>
<td>teal/white</td>
</tr>
<tr>
<td>Terbutaline – Bricanyl®</td>
<td>blue/white</td>
</tr>
<tr>
<td>ICS</td>
<td></td>
</tr>
<tr>
<td>Fluticasone – Flovent®</td>
<td>orange/peach</td>
</tr>
<tr>
<td>Budesonide – Pulmicort®</td>
<td>white/brown</td>
</tr>
<tr>
<td>Combined Long-Acting β-Agonist + ICS</td>
<td>purple discus</td>
</tr>
<tr>
<td>Fluticasone/Salmeterol – Advair®</td>
<td>red/white</td>
</tr>
<tr>
<td>Budesonide/Formoterol – Symbicort®</td>
<td>red/white</td>
</tr>
<tr>
<td>Ipratropium/Albuterol – Combivent®</td>
<td>clear/orange</td>
</tr>
<tr>
<td>Anticholinergics</td>
<td></td>
</tr>
<tr>
<td>Ipratropium – Atrovent®</td>
<td>clear/green</td>
</tr>
<tr>
<td>Tiotropium – Spiriva®</td>
<td>white/turquoise</td>
</tr>
</tbody>
</table>

---

**More About Inhalers**

- Aerosols (puffers=MDI, MDI + spacer)
- MDIs should be used with spacers to:
  - Reduce side effects
  - Improve amount inhaled
  - Increase efficiency of use
- Dry Poweder Inhalers (discus, turbohaler, and diskhaler) require deep and fast breathing (may not be ideal for children)
- Nebulizers can be used to convert liquid medications into a fine mist: recommended for use if contraindications to MDIs

---

**Differential Diagnosis of Wheezing**

- Allergies, anaphylaxis
- Asthma, reactive airway disease
- GERD
- Infections (bronchitis, pneumonia)
- Obstructive Sleep Apnea
- COPD
- Less common: congestive heart disease, foreign body, malignancy, cystic fibrosis, vocal cord dysfunction

---

**Self-Management Asthma and COPD**

**Education and Written Action Plan**

- Education is a key component in management of asthma and COPD
- Guided self-management combining education, regular medical review, self-assessment, and written action plan have been shown to reduce hospitalizations, ER visits, and missed days at work or school
- Sample action plans available online: [http://www.respiratoryguidelines.ca](http://www.respiratoryguidelines.ca)
increased PSA in a younger man is more often due to cancer than other causes
abnormal DRE or PSA should trigger further assessment
discuss test with men at increased risk of prostate cancer (FHx, African ancestry) or who are concerned about development of prostate cancer
decision to test PSA in an asymptomatic man should involve discussion about the risks and possible benefits
other tests
• Cr, BUN
• post-void residual volume by ultrasound
• urodynamic studies, renal ultrasound
• patient voiding diary
tests NOT recommended as part of routine initial evaluation include:
• cystoscopy
• cytology
• prostate ultrasound or biopsy
• IVP
• urodynamic studies

Table 11. Symptoms and Complications of BPH

<table>
<thead>
<tr>
<th>Obstructive Symptoms</th>
<th>Irritative Symptoms</th>
<th>Late Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hesitancy (difficulty starting urine flow)</td>
<td>Urgency</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Diminution in size and force of urinary stream</td>
<td>Frequency</td>
<td>Loss of renal concentrating ability</td>
</tr>
<tr>
<td>Stream interruption (double voiding)</td>
<td>Nocturia</td>
<td>Systemic acidosis</td>
</tr>
<tr>
<td>Urinary retention (bladder does not feel completely empty)</td>
<td>Urgine incontinence</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Post-void dribbling</td>
<td>Dysuria</td>
<td></td>
</tr>
<tr>
<td>Overflow incontinence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nocturia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Management
• referral to urologist if moderate/severe symptoms
• conservative: for patients with mild symptoms or moderate/severe symptoms considered by the patient to be non-bothersome
  • fluid restriction (avoid alcohol and caffeine)
  • avoidance/monitoring of certain medications (e.g. antihistamines, diuretics, antidepressants, decongestants)
  • pelvic floor/Kegel exercises
  • bladder retraining (scheduled voiding)
• pharmacological: for moderate/severe symptoms
  • α-receptor antagonists (e.g. terazosin [Hytrin®], doxazosin [Cardura®], tamsulosin [Flomax®], alfuzosin [Xatral®])
    • relaxation of smooth muscle around the prostate and bladder neck
  • 5α-reductase inhibitor (e.g. finasteride [Proscar®])
    • only for patients with demonstrated prostatic enlargement due to BPH
    • inhibits enzyme responsible for conversion of testosterone into dihydrotestosterone (DHT) thus reducing growth of prostate
  • phytotherapy (e.g. saw palmetto berry extract, Pygeum africanum)
    • more studies required before this can be recommended as standard therapy
    • considered safe
• surgical
  • TURP (transurethral resection of the prostate), TUIP (transurethral incision of the prostate, for prostates <30 g)
  • absolute indications: failed medical therapy, intractable urinary retention, benign prostatic obstruction leading to renal insufficiency
  • complications: impotence, incontinence, ejaculatory difficulties (retrograde ejaculation), decreased libido

Bronchitis (Acute)

Definition
• acute infection of the tracheobronchial tree causing inflammation leading to bronchial edema and mucus formation

Epidemiology
• 5th most common diagnosis in family medicine, most common is URTI

Etiology
• 80% viral: rhinovirus, coronavirus, adenovirus, influenza, parainfluenza, respiratory syncytial virus (RSV)
• 20% bacterial: M. pneumoniae, C. pneumoniae, S. pneumoniae

Differential Diagnosis
• Prostate cancer
• Urethral obstruction
• Bladder neck obstruction
• Neurogenic bladder
• Overactive bladder
• Cystitis
• Prostatitis

Differential Diagnosis of Bronchitis
• URTI
• Asthma
• Acute exacerbation of chronic bronchitis
• Sinusitis
• Pneumonia
• Bronchiolitis
• Pertussis
• Environmental/occupational exposures
• Post-nasal drip
• Others: GERD, CHF, cancer, aspiration syndromes, CF, foreign body
Investigations
- acute bronchitis is typically a clinical diagnosis
- sputum culture/Gram stain is not very informative
- CXR if suspect pneumonia (cough $>3$ wk, abnormal vital signs, localized chest findings) or CHF
- PFT with methacholine challenge if suspect asthma

Management
- primary prevention: frequent hand washing, smoking cessation, avoid irritant exposure
- symptomatic relief: rest, fluids ($3-4$ L/d when febrile), humidity, analgesics and antitussives as required
- bronchodilators may offer improvement of symptoms (e.g. salbutamol)
- current literature does not support routine antibiotic treatment for the management of acute bronchitis because it is most likely to be caused by a viral infection
  - antibiotics may be useful if elderly, comorbidities, suspected pneumonia, or if the patient is toxic (refer to Antimicrobial Quick Reference, FM54)
  - antibiotics in children show no benefit

Chest Pain
- see Cardiology and Cardiac Surgery, C4 and Emergency Medicine, ER21

Differential Diagnosis

<table>
<thead>
<tr>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>GI</th>
<th>MSK/Neuro</th>
<th>Psychologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina*</td>
<td>Hemothorax*</td>
<td>Cholecystitis</td>
<td>Arthritis</td>
<td>Anxiety</td>
</tr>
<tr>
<td>Aortic dissection*</td>
<td>Lung CA</td>
<td>Esophageal spasm</td>
<td>Costochondritis</td>
<td>Depression</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>PE*</td>
<td>GERD</td>
<td>Herpes zoster</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Mí*</td>
<td>Pneumonia</td>
<td>Hepatitis</td>
<td>Intercostal strain</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>Pneumothorax*</td>
<td>Perforated viscus*</td>
<td>Rib fractures</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>Pericarditis*</td>
<td>Pulmonary HTN</td>
<td>PUD</td>
<td>Trauma</td>
<td>Anxiety</td>
</tr>
</tbody>
</table>

*Emergency

Investigations
- ECG, CXR, and others if indicated (cardiac enzymes, d-dimers, liver function tests [LFTs], etc.)
- refer to ED if suspect serious etiology (e.g. aortic dissection, MI)

Management of Common Causes of Chest Pain
- angina/ischemic heart disease
  - nitroglycerin (NTG): wait 5 min between sprays and if no effect after 3 sprays, send to ED
  - myocardial infarction
    - ASA (160-325 mg, chewed stat), clopidogrel (Plavix*), LMWH (enoxaparin), morphine, oxygen, NTG
    - $\pm$ reperfusion therapy with fibrinolytics (e.g. tPA, RPA, TNK, or SK) if within 12h (ideally $<30$ min) or percutaneous intervention (cath lab) if $<90$ min
    - start $\beta$-blocker (e.g. metoprolol starting dose 25 mg PO q6h or bid, titrating to HR goal of 55–60 bpm)
- endocarditis: antibiotic choice is based on whether patient has a native or prosthetic heart valve as well as culture and sensitivity results
- GERD: antacids, $H_2$ blockers, PPIs, patient education
- costochondritis: NSAIDs

Treatment of Stable Ischemic Heart Disease
- see Cardiology and Cardiac Surgery, C28
Common Cold (Acute Rhinitis)

- **Definition**
  - viral URTI with inflammation

- **Epidemiology**
  - most common diagnosis in family medicine, peaks in winter months
  - incidence: adults = 2-4/yr, children = 6-10/yr
  - organisms
    - mainly rhinoviruses (30-35% of all colds)
    - others: coronavirus, adenovirus, RSV, influenza, parainfluenza, coxsackie virus
  - incubation: 1-5 d
  - transmission: person-person contact via secretions on skin/objects and by aerosol droplets

- **Risk Factors**
  - psychological stress, excessive fatigue, allergic nasopharyngeal disorders, smoking, sick contacts

- **Clinical Features**
  - symptoms
    - local: nasal congestion, clear to mucopurulent secretions, sneezing, sore throat, conjunctivitis, cough
    - general: malaise, headache, myalgias, mild fever
  - signs
    - boggy and erythematous nasal/oropharyngeal mucosa, enlarged lymph nodes
  - normal chest exam
  - complications
    - secondary bacterial infection: otitis media, sinusitis, bronchitis, pneumonia
    - asthma/COPD exacerbation

- **Differential Diagnosis**
  - allergic rhinitis, pharyngitis, influenza, laryngitis, croup, sinusitis, bacterial infections

- **Management**
  - patient education
    - symptoms peak at 1-3 d and usually subside within 1 wk
    - cough may persist for days to weeks after other symptoms disappear
    - no antibiotics indicated because of viral etiology
    - secondary bacterial infection can present within 3-10 d after onset of cold symptoms
  - prevention
    - frequent hand washing, avoidance of hand to mucous membrane contact, use of surface disinfectant
    - yearly influenza vaccination
  - symptomatic relief
    - rest, hydration, gargling warm salt water, steam, nasal irrigation (spray/pot)
    - analgesics and antipyretics: acetaminophen, ASA (not in children because risk of Reye's syndrome)
    - cough suppression: dextromethorphan or codeine if necessary (children under 6 yr of age should not use any cough/cold medications)
    - decongestants, antihistamines
    - zinc lozenge use may help to reduced the duration of cold symptoms
  - patients with reactive airway disease will require increased use of bronchodilators and inhaled steroids

Concussion/Mild Traumatic Brain Injury

- **Definition**
  - see Neurosurgery, NS30, and Emergency Medicine, ER9
  - a useful tool for the assessment of individuals and athletes with concussion is the Sport Concussion Assessment Tool, 3rd edition (SCAT3), Br J Sports Med 2013 47: 259

Contraception

- **Definition**
  - see Gynecology, GY16

**EMERGENCY CONTRACEPTION**

- hormonal EC (Yuzpe® or Plan B®, usually 2 doses taken 12 h apart) or post-coital IUD insertion
- hormonal EC is effective if taken within 72 h of unprotected intercourse (reduces chance of pregnancy by 75-85%), most effective if taken within 24 h, does not affect an established pregnancy
• post-coital IUDs inserted within 5 d of unprotected intercourse are significantly more effective than hormonal EC (reduces chance of pregnancy by ~99%)
• pregnancy test should be performed if no menstrual bleeding within 21 d of either treatment
• advance provision of hormonal EC increases the use of EC without decreasing the use of regular contraception
• pharmacists across Canada can dispense Plan B* OTC

Dementia (Major Neurocognitive Disorder)

• see Psychiatry, PS21

Epidemiology
• 10% in patients over the age of 65, 25% in patients over the age of 85, 50% in patients over the age of 90
• prevalence increases with age, Down syndrome, and head trauma
• differential diagnosis: Alzheimer's dementia, vascular dementia, Lewy-Body dementia, frontotemporal dementia

Investigations
• history, physical exam, MMSE, MOCA (best screening test), dementia quick screen (see sidebar)
• investigations are completed to exclude reversible causes of dementia and should be selected based on the clinical circumstances
• CBC, liver enzymes, TSH, renal function tests, serum electrolytes, serum calcium, serum glucose, vitamin B12, folate, VDRL, HIV, head CT

Management
• treat and prevent reversible causes
• provide orientation cues (e.g. calendars, clocks) and optimize vision and hearing
• family education, counselling, and support (respite programs, group homes)
• pharmacologic therapy: NMDA receptor antagonists and cholinesterase inhibitors slow rate of cognitive decline; low-dose neuroleptics and antidepressants can be used to treat behavioral and emotional symptoms
• 20% of patients develop clinical depression, most commonly seen in vascular dementia

Depression

• see Psychiatry, PS10

Etiology
• often presents as non-specific complaints (e.g. sleep disturbance, chronic fatigue, pain)
• depression is a clinical diagnosis and tests are done in order to rule out other causes of symptoms
• 2/3 of depressed persons may not receive appropriate treatment for their depression
• identification and early treatment improve outcomes

Screening Questions
• new Canadian Task Force on Preventive Health Care guidelines (2013) recommends against routine screening
• although routine screening is not recommended, useful questions for at-risk populations are:
  • “Are you depressed?” (high specificity and sensitivity)
  • “Have you lost interest or pleasure in the things you usually like to do?” (anhedonia)
  • “Do you have problems sleeping?”
• for geriatric population, use the Geriatric Depression Scale (GDS) short form for screening
Assessment
- risk factors: see Psychiatry, PS11
- personal or family history of depression
- medications and potential substance abuse problems
- high risk suicidality/homicidality
  - fill out Form 1 (in Ontario): application by physician to hospitalize a patient against his/her will for psychiatric assessment (up to 72 h)
  - functional impairment (e.g. work, relationships)
- at least 5 out of 9 criteria including at least one of anhedonia or depressed mood ≥ 2 wk for actual diagnosis to be met (see sidebar)
- validated depression rating scales: Beck’s depression inventory, Zung’s self-rating depression scale, Children’s depression inventory, Geriatric Depression Scale, Personal Health Questionnaire Depression Scale (PHQ-9)
- routine medical workup (physical exam, CBC, TSH, ferritin, folate, B₁₂, electrolytes, urinalysis, glucose, etc.)

Treatment
- goal: full remission of symptoms and return to baseline psychosocial function
- phases of treatment
  - acute phase (8-12 wk): relieve symptoms and improve quality of life
  - maintenance phase (6-12 mo after symptom resolution): prevent relapse/recurrence, must stress importance of continuing medication treatment for full duration to patients
- treatment can consist of pharmacotherapy alone or psychotherapy alone
- combination of antidepressant drug therapy and psychotherapy results in synergistic effects
- treatment of youth (age 10-21)
  - for mild depression, a period of active support and monitoring before initiating treatment is recommended
  - fluoxetine is first line among SSRIs (most evidence)
  - monitor closely for adverse effects such as suicidal ideation and behavior
  - psychotherapy
  - CBT or interpersonal therapy (IPT) alone can be used for mild depression
  - psychotherapy plus medication is recommended for moderate to severe depression
  - treatment should continue for at least 6 months
  - ongoing management should include assessment in key domains (school, home, social setting)
  - reassessment and referral recommended if no improvement after 6-8 wk of treatment
- for adolescents with moderate/severe depression and coexisting psychosomatic and/or substance abuse, consider referral

Table 13. Common Medications

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Action</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>paroxetine (Paxil)</td>
<td>Block serotonin reuptake</td>
<td>Sexual dysfunction (impotence, decreased libido, delayed ejaculation, anorgasmia), headache, GI upset, weight loss, tremors, insomnia, fatigue, increase GI interval (baseline ECG is suggested)</td>
<td>First line therapy for youth is fluoxetine; paroxetine is not recommended for youth (controversial)</td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor)</td>
<td>Block serotonin and NE reuptake</td>
<td>Insomnia, tremors, tachycardia, sweating</td>
<td></td>
</tr>
<tr>
<td>SDRI</td>
<td>bupropion (Wellbutrin)</td>
<td>Block dopamine and NE reuptake</td>
<td>Headache, insomnia, nightmares, seizures, less sexual dysfunction than SSRIs</td>
<td>Often chosen for lack of sexual side effects, can be used for augmentation of anti-depressant effects with other classes of medication</td>
</tr>
<tr>
<td>TCA</td>
<td>amitriptyline (Elavil)</td>
<td>Block serotonin and NE reuptake</td>
<td>Sexual dysfunction, weight gain, tremors, tachycardia, sweating</td>
<td>Narrow therapeutic window, lethal in overdose</td>
</tr>
</tbody>
</table>

Prognosis
- up to 40% resolve spontaneously within 6-12 mo
- risks of recurrence: 50% after 1 episode; 70% after 2 episodes; 90% after 3 episodes

Diabetes Mellitus
- see Endocrinology, E7

Definition
- a group of metabolic diseases characterized by persistent hyperglycemia.

Classification
- type 1: primarily a result of pancreatic β-cell destruction
- type 2: characterized by insulin resistance
- GDM: glucose intolerance with onset or first recognition during pregnancy

Criteria for Depression (≥5/9 with at least one of anhedonia or depressed mood for ≥ 2 wk)

M-SIGECAPS
M Depressed Mood
S Increased/decreased Sleep
I Decreased Interest
G Guilt
E Decreased Energy
C Decreased Concentration
A Increased/decreased Appetite and weight
P Psychomotor agitation/retardation
S Suicidal ideation

Combined Pharmacotherapy and Psychological Treatment for Depression: A Systematic Review Arch Gen Psychiatry 2004;61:714-719

Study: Systematic review of randomized clinical trials.
Patients: 16 trials comprising 1,842 patients.
Intervention: Antidepressant treatment alone vs. combination of psychological intervention and antidepressant therapy.
Main Outcomes: Efficacy of and adherence to therapy.
Results: Overall, combined therapy was significantly more effective than antidepressant therapy alone (OR 1.88; 95% CI 1.38-2.52), however there was no difference in the rate of dropouts and non-responders in either treatment arm. In studies lasting > 12 wk, combined therapy showed a reduction in dropouts compared to non-responders (OR 0.59; 95% CI 0.39-0.88).
Epidemiology
• major health concern, affecting up to 10% of Canadians
• incidence of type 2 DM is rising dramatically as a result of an aging population, rising rates of obesity, and sedentary lifestyles
• leading cause of new-onset blindness and renal dysfunction
• Canadian adults with DM are twice as likely to die prematurely, compared to persons without DM

Risk Factors
• type 1 DM
  ▪ personal or family history of autoimmune disease
• type 2 DM
  ▪ first degree relative with DM
  ▪ age ≥40 yr
  ▪ obesity (especially abdominal), HTN, hyperlipidemia, CAD, vascular disease
  ▪ prior GDM, macrosomic baby (>4 kg)
  ▪ PCOS
  ▪ history of IGT or IFG
  ▪ presence of complications associated with DM
  ▪ presence of associated diseases: PCOS, acanthosis nigricans, psychiatric disorders, HIV
  ▪ medications: glucocorticoids, atypical antipsychotics, HAART
• both
  ▪ member of a high risk population (e.g. Aboriginal, Hispanic, Asian, or African descent)

Diagnosis
• persistent hyperglycemia is the hallmark of all forms of DM

Table 14. Diagnosis of Prediabetes and Diabetes

<table>
<thead>
<tr>
<th>Condition</th>
<th>Diagnostic Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>DM</td>
<td>One of the following on 2 occasions:</td>
</tr>
<tr>
<td></td>
<td>• Random BG ≥11.1 mmol/L (200 mg/dL) with symptoms of DM (fatigue, polyuria, polydipsia, unexplained weight loss) OR</td>
</tr>
<tr>
<td></td>
<td>• Fasting BG ≥7.0 mmol/L (126 mg/dL) OR</td>
</tr>
<tr>
<td></td>
<td>• BG 2 h post 75 g OGGT ≥11.1 mmol/L (200 mg/dL) OR</td>
</tr>
<tr>
<td></td>
<td><strong>If asymptomatic (and meet any of the above criteria) a repeat test must be done to confirm the diagnosis. If symptomatic (fatigue, polyuria, polydipsia, unexplained weight loss), the diagnosis is made with one test.</strong></td>
</tr>
<tr>
<td>Impaired Fasting Glucose (IFG)</td>
<td>Fasting BG = 6.1-6.9 mmol/L (110-124 mg/dL)</td>
</tr>
<tr>
<td>Impaired Glucose Tolerance (IGT)</td>
<td>BG 2 h post 75 g OGGT = 7.8-11.0 mmol/L (141-198 mg/dL)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>HbA1c = 6.0-6.4%</td>
</tr>
</tbody>
</table>

Screening
• type 2 DM
  ▪ FBG in everyone ≥40 q3yr, or at high risk using the CANRISK calculator
  ▪ more frequent and/or earlier testing if presence of ≥1 risk factor (see above)
• GDM (see Obstetrics, OB27)
  ▪ all pregnant women between 24-28 wk gestation

Goals of Therapy

Table 15. Goals of Therapy in Diabetes

| General                     | Avoid complications (e.g. ketoacidosis, hyperglycemia, infection)                      |
|                            | Prevent long-term complications (microvascular and macrovascular)                      |
|                            | Minimize negative sequelae associated with therapies (e.g. hypoglycemia, weight gain) |
| Fasting or Preprandial BG  | Ideal: 4-7 mmol/L (72-126 mg/dL)                                                     |
|                            | Suboptimal: 7.1-10 mmol/L (128-180 mg/dL); action may be required                     |
|                            | Inadequate: >10.0 mmol/L (180 mg/dL); action required                                  |
|                            | Frail Elderly: target is 5-12 mmol/L                                                 |
| HbA1c                      | ≤7% or ≤6.5% in some type 2 DM patients at risk for nephropathy                        |
|                            | Suboptimal: 7-8.4%                                                                    |
|                            | Inadequate: >8.4%                                                                    |
|                            | Frail elderly, advanced co-morbidities, recurrent severe hypoglycemia or hypoglycemia unawareness: target is 7.1-8.5%   |
| 2 h Postprandial BG        | 5-10 mmol/L (90-180 mg/dL) if HbA1c target met                                       |
|                            | 5-8 mmol/L (90-144 mg/dL) if HbA1c target not met                                    |
|                            | Frail elderly: use clinical judgment                                                  |
| Blood Pressure             | <130/80 in adults (DM and HTN guidelines)                                             |
| Lipids                     | LDL <2.0 mmol/L (36 mg/dL)                                                           |
Assessment and Monitoring

Table 16. Assessment and Monitoring

<table>
<thead>
<tr>
<th>History</th>
<th>Initial Assessment</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms of hyperglycemia, ketoacidosis, hypoglycemia</td>
<td>DM-directed history</td>
<td>Screen for awareness and frequency of hyperglycemia and DKA</td>
<td></td>
</tr>
<tr>
<td>Past medical history</td>
<td>Screen for awareness and frequency of hyperglycemia and DKA</td>
<td>Glucose monitoring</td>
<td></td>
</tr>
<tr>
<td>Functional inquiry</td>
<td>Glucose monitoring</td>
<td>Use of insulin and oral agents</td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>Use of insulin and oral agents</td>
<td>Smoking cessation</td>
<td></td>
</tr>
<tr>
<td>Risk factors</td>
<td>Sexual function</td>
<td>Lifestyle</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td>Lifestyle counselling</td>
<td>Screen for depression</td>
<td></td>
</tr>
<tr>
<td>Sexual function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Physical Exam</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>General: Ht, Wt, BMI, BP, WC</td>
<td>Wt, BP, BMI, WC</td>
<td>Foot exam for sensation (using a 10 g monofilament), ulcers or infection</td>
</tr>
<tr>
<td>Head and neck: fundoscopy, thyroid exam</td>
<td></td>
<td>Remainder of exam as per PHE</td>
</tr>
<tr>
<td>Cardiovascular exam: signs of PVD, pulses, bruits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal exam (e.g. for organomegaly)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hand/foot/skin exam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurological exam</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Investigations</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBG, HbA1c, fasting lipids, Ccr, microalbumin:creatinine ratio</td>
<td>HbA1c q3mo</td>
<td>Fasting lipid profile</td>
</tr>
<tr>
<td>Baseline ECG, repeat testing q2yrs for those at high risk</td>
<td>FBG as needed</td>
<td>Annual random ACR and eGFR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Management</th>
<th>q2-4mo</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nutritional and physical education</td>
<td>Assess progress towards long-term complications</td>
<td>Calibrate home glucose monitor</td>
</tr>
<tr>
<td>Consider referral to DM education program if available</td>
<td>Adjust treatment plan if necessary</td>
<td>Arrange retinopathy screening</td>
</tr>
<tr>
<td>Monitoring BG: explain methods and frequency</td>
<td></td>
<td>Influenza vaccination annually</td>
</tr>
<tr>
<td>Medication counselling: oral hypoglycemics and/or insulin, method of administration, dosage adjustments</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumococcal vaccination</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ophthalmology consult</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type 1 DM within 5 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>type 2 DM at diagnosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Nonpharmacologic Management

- **diet**
  - all diabetics should see a registered dietician for nutrition counselling
  - can reduce HbA1c by 1-2%
  - moderate weight loss (5%) improves glycemic control and CVD risk factors
  - decrease combined saturated fats and trans-fatty acids to <10% of calories
  - avoid simple sugars, choose low glycemic-index foods, ensure regularity in timing and spacing of meals
  - physical activity and exercise
    - at least 150 min of aerobic exercise per wk, plus 2 sessions per wk of resistance exercise is recommended
    - encourage 30-45 min of moderate exercise 4-7 d/wk
    - promote cardiovascular fitness: increases insulin sensitivity, lowers BP, and improves lipid profile
  - if insulin treated, may require alterations of diet, insulin regimen, injection sites, and self-monitoring

Self-Monitoring of Blood Glucose

- type 1 DM: 3 or more self-tests/d is associated with a 1% reduction in HbA1c
- type 2 DM: recommendations vary based on treatment regimen (e.g. insulin dependent requires more frequent monitoring – refer to 2013 Canadian Practice Guidelines)
- if FBG >14 mmol/L, perform ketone testing to rule out DKA
- if bedtime level is <7 mmol/L, have bedtime snack to reduce risk of nocturnal hypoglycemia

Dietary Advice for Treatment of Type 2 DM in Adults


A meta-analysis, using 36 articles reporting a total of 18 trials following 1,467 participants, showed that there is no high quality data on the efficacy of dietary treatment of type 2 DM. After 6 and 12 mo, adoption of exercise improved HbA1c.

Calculated Total Insulin Required

<table>
<thead>
<tr>
<th>Type 1 DM</th>
<th>Type 2 DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-0.7 units/kg/d</td>
<td>0.3 units/kg/d</td>
</tr>
</tbody>
</table>

Calculate Total Insulin Required
**Figure 8. Types of insulin preparation**

![Diagram of plasma insulin levels over 24 hours after injection.](image)

**Clinical Assessment**

1. **Lifestyle intervention** (initiation of nutrition therapy and physical activity)
2. **HbA1c < 9.0%**
   - Initiate **metformin**
3. **HbA1c ≥ 9.0%**
   - Initiate **pharmacotherapy** immediately without waiting for effect from lifestyle interventions.
   - Consider initiating **metformin** concurrently with another agent from a different class; or initiate insulin
4. **Symptomatic hyperglycemia**
   - Initiate **insulin ± metformin**

**Add an agent best suited to the individual based on the advantages/disadvantages listed below**

<table>
<thead>
<tr>
<th>Class</th>
<th>HbA1c</th>
<th>Hypoglycemia</th>
<th>Other Advantages</th>
<th>Other Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Glucosidase Inhibitor</td>
<td>↓</td>
<td>Rare</td>
<td>Improved postprandial control</td>
<td>GI side effects</td>
</tr>
<tr>
<td>Incretin Agent:</td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>↓</td>
<td>Rare</td>
<td>Improved postprandial control</td>
<td>New agent (unknown long-term safety)</td>
</tr>
<tr>
<td>Insulin</td>
<td>↓</td>
<td>Yes</td>
<td>No dose ceiling</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Insulin Secretagogue</td>
<td>↓</td>
<td>Yes*</td>
<td>Improved postprandial control</td>
<td>Requires tid to qid dosing</td>
</tr>
<tr>
<td>Meglitinide</td>
<td>↑</td>
<td>Yes</td>
<td>Improved postprandial control</td>
<td>Requires tid to qid dosing</td>
</tr>
<tr>
<td>Sulfonylurea</td>
<td>↓</td>
<td>Yes</td>
<td>Improved postprandial control</td>
<td>Requires tid to qid dosing</td>
</tr>
<tr>
<td>DPP-4 – dipeptidyl peptidase-4</td>
<td>↓</td>
<td></td>
<td>1.0-2.0% decrease in A1c</td>
<td></td>
</tr>
<tr>
<td>TZD</td>
<td>↓</td>
<td>Rare</td>
<td>Weight gain</td>
<td>Edema, rare CHF, rare fractures in females</td>
</tr>
<tr>
<td>Weight Loss Agent</td>
<td>↓</td>
<td>None</td>
<td>Weight loss</td>
<td>GI side effects (orlistat) Increased heart rate/BP (sibutramine)</td>
</tr>
</tbody>
</table>

**Timely adjustments**

- Add another drug from a different class; or
- Add bedtime basal insulin to other agent(s); or
- Intensify insulin regimen

**Figure 9. Management of hyperglycemia in type 2 diabetes**

Hypoglycemic Agents (Type 2 DM)
- oral
  - biguanide: metformin (Glucophage®)
  - thiazolidinedione: troglitazone (Rezulin®), rosiglitazone (Avandia®)
  - α-glucosidase inhibitor: acarbose (Precose®)
  - nonsulfonylureas: nateglinide (Starlix®), repaglinide (Gluconorm®)
  - sulfonylureas: glyburide (DiaBeta®), glimepiride (Amaryl®), gliclazide (Diamicron®)
  - DPP-4 inhibitor: sitagliptin (Januvia®)
- injectable
  - GLP-1 analogue: liraglutide (Victoza®)

Other Medications Used in DM
- ACEI or ARB in those with any of
  - clinical macrovascular disease
  - age ≥55 years
  - age <55 and microvascular complications
- statin in those with any of
  - clinical macrovascular disease
  - age ≥40 years
  - age <40 and any of the following:
    - diabetes duration >15 years and age >30 years
    - microvascular complications
    - other cardiovascular risk factors
- low dose ASA (81-325 mg)
  - for secondary prevention in people with established CVD (NOT to be used routinely for primary prevention)

Dizziness
- see Otolaryngology, OT12

Epidemiology
- 70% see general practitioners initially; 4% referred to specialists
- frequency proportional to age; commonest complaint of ambulatory patients age >75

Differential Diagnosis

![Dizziness Diagram](image)

Vertigo (vestibular)
- Objective (external world seems to revolve around individual) or subjective (individual revolves in space)
  - Central (15%)
    - Brainstem
    - Cerebellar
  - Peripheral (85%)
    - Inner ear
    - Vestibular nerve

Psychogenic
- Diagnosis of exclusion

Vascular
- Diagnosis of exclusion
  - Basilar migraine
  - TIA
  - Orthostatic hypotension
  - Stokes-Adams syndrome
  - Arrhythmia
  - CHF
  - Aortic stenosis
  - Vasovagal episodes
  - Metabolic causes

Ocular
- Decreased visual acuity

DDx of Vertigo

<table>
<thead>
<tr>
<th>BPPV</th>
<th>Labyrinthitis</th>
<th>Ménière’s</th>
<th>Acoustic Neurina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outer</td>
<td>sudden</td>
<td>sudden</td>
<td>gradual</td>
</tr>
<tr>
<td>Duration</td>
<td>seconds</td>
<td>days</td>
<td>min-hours</td>
</tr>
<tr>
<td>Hearing</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Tinnitus</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neuro Sx</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Figure 10. Differential diagnosis of dizziness

History
- clarify type of dizziness: vertigo, pre-syncope, disequilibrium, light-headedness
- duration (seconds, minutes, hours, days, weeks, or persistent)
- exacerbations
  - worse with head movement or eye closure (vestibular)
  - no change with head movement and eye closure (nonvestibular)
  - worse with exercise (cardiac/pulmonary causes)
• associated symptoms
  - neurologic (central)
    - transient diplopia, dysphagia, dysarthria, ataxia (TIA, VBI, migraine)
    - persistent headache, alterations in level of consciousness, sensory and/or motor deficits (CNS)
  - audiologic (peripheral)
    - hearing loss, tinnitus, otalgia, aural fullness
  - others
    - N/V (peripheral vestibular disorders)
    - SOB, palpitations (hyperventilation, cardiac problem)
• general medical history
  - HTN, DM, heart disease, fainting spells, seizures, cerebrovascular disease, migraines
  - ototoxic drugs: aminoglycosides (gentamicin, streptomycin, tobramycin), erythromycin, ASA, antimalarials
  - hypotension (secondary to diuresis): furosemide, caffeine, alcohol
  - depression/anxiety: can present with light-headedness

Physical Exam/Investigations
• syncopal
  - cardiac (orthostatic changes in vitals), peripheral vascular, and neurologic exams
  - blood work, ECG, 24 h Holter, treadmill stress test, loop ECG, tilt table testing, carotid, and vertebral doppler, EEG
• vertiginous
  - ENT and neurologic exams
  - Dix-Hallpike, consider audiometry and MRI if indicated
• non-syncopal, non-vertiginous
  - assess gait, vision and test for neuropathy
  - cardiac and neurologic exams
  - 3-min hyperventilation trial (patient is coached to hyperventilate until patient becomes dizzy to identify if symptoms are reproducible and confirm that hyperventilation is the etiology of the symptoms), ECG, EEG
  - Romberg test: test for disequilibrium (patient sways towards the side of vestibular dysfunction)

Treatment
• guided by history, physical exam, and investigations
• include education, lifestyle modification, physical maneuvers (e.g. Epley for BPPV), symptomatic management (e.g. antiemetics), pharmacotherapy, and surgery
• refer when significant central disease is suspected, when vertigo of peripheral origin is persistent (lasting >2-4 wk), or if atypical presentation

Domestic Violence/Elder Abuse

INTIMATE PARTNER VIOLENCE

Definition
• includes physical, sexual, emotional, psychological, and financial abuse
  (see Emergency Medicine, ER28)

Epidemiology
• lifetime prevalence of intimate partner violence against women is between 25-30%
• women who experience abuse have increased rates of injury, death, and health consequences including 50-70% increase in gynecological, central nervous system, stress-related problems
• occurs in all socioeconomic, educational, and cultural groups with increased incidence in pregnancy, disabled women, and 18-24 age group
• 25-50% chance of child abuse or neglect in families where partner abuse occurs
• physician recognition rates as low as 5%

Presentation
• multiple visits with vague, ill-defined complaints such as: headaches, gastrointestinal symptoms, insomnia, chronic pain, hyperventilation
• may also present with injuries inconsistent with history

Management
• screen ALL patients
  - always have a high index of suspicion
  - asking about abuse is the strongest predictor of disclosure
  - several screening tools (see sidebar) exist to identify victims of partner violence
  - make sure to determine the victim’s level of immediate and long-term danger and ask if there are weapons in the house
  - ensure patient safety
  - victim most at risk for homicide when attempting to leave home or following separation

Screening Instruments for Domestic Violence
A) Woman Abuse Screening Tool (WAST)-SHORT
  1. In general how would you describe your relationship?
     a. A lot of tension
     b. Some tension
     c. No tension
  2. Do you and your partner work out arguments with...?
     a. Great difficulty
     b. Some difficulty
     c. No difficulty
  Endorsing either question 1 (“a lot of tension”) or question 2 (“great difficulty”) makes intimate partner violence exposure likely

B) HITS
  How often does your partner:
  1. Physically hurt you?
  2. Insult you?
  3. Threaten you with harm?
  4. Scream or curse at you?
  Each question on HITS to be answered on a 5 point scale ranging from 1 (= never) to 5 (= frequently)
  A total score of 10.5 is significant
• provide community resources
  ▪ safety planning includes ensuring that there is access to an exit in the home, establishing a safe place to go and having money, clothes, keys, medications, important documents, and other emergency items prepared should the patient need to leave quickly
  ▪ shelter or helpline number with legal advocacy and counselling services
  ▪ involve social workers or domestic violence advocates
• appointment for follow-up to assess whether condition is better or worse
• reassure patient she/he is not to blame and that the assault is a crime
  ▪ goal is to convey the message that “As your doctor, I am concerned for your safety” and “Your partner has a problem that he/she needs help with” and “I want to help you”
  ▪ reporting suspected or known child abuse is mandatory
  ▪ spousal abuse is a criminal act, but not reportable without the woman’s/man’s permission
• DOCUMENT all evidence of abuse-related visits for medico-legal purposes

ELDER ABUSE
• see Geriatric Medicine, GM4

Dyspepsia
• see Gastroenterology, G10

Definition and Clinical Features
• defined as epigastric pain or discomfort
• can be associated with fullness, belching, bloating, heartburn, food intolerance, N/V

Epidemiology
• annual incidence 1-2%, prevalence 20-40%

Etiology
• common: functional, PUD, GERD, gastritis
• others: cholelithiasis, irritable bowel syndrome, esophageal or gastric cancer, pancreatitis, pancreatic cancer, Zollinger-Ellison syndrome, and abdominal angina

History
• symptoms may not be useful in finding cause
• association with food, anorexia, N/V, alcohol, NSAID use
• alarm symptoms: vomiting, bleeding/anemia, abdominal mass, dysphagia (VBAD)

Investigations and Management
• for new onset dyspepsia, test for H. pylori is commonly done using the urea breath test or serology
  ▪ upper endoscopy (preferred), upper GI series (not in patients with alarm symptoms)
  ▪ lifestyle modifications: dietary changes, smaller and more frequent meals, avoid supine position right after meals, decreased EtOH consumption, smoking cessation
  ▪ pharmacologic treatment
  ▪ gastric acid suppression: H₂ blockers, PPI’s; both are effective for PUD and GERD
  ▪ prokinetics: e.g. Metoclopramide; effective for functional dyspepsia
  ▪ H. pylori eradication
  ▪ do not keep patients on PPI without at least 1 trial off the medication per year.
• for non-responders, gastroscopy should be considered

Dyspnea
• see Respirology, R3 and Emergency Medicine, ER26

Definition
• term used to characterize a subjective experience of breathing discomfort

History and Physical Exam
• history
  ▪ cough, sputum, hemoptysis, wheezing, chest pain, palpitations, dizziness, edema
  ▪ asthma, allergy, eczema, ASA/NSAID sensitivity, nasal polyps
  ▪ constitutional symptoms
  ▪ smoking, recreational drugs, medications
  ▪ occupational exposure, environmental exposure (e.g. pets, allergens, smoke)
  ▪ travel and birth place
  ▪ FHx of atopy
  ▪ previous CXR or PFTs
• physical exam: vitals, respiratory, precordial, HEENT, signs of anemia/liver failure/heart failure

H. pylori Eradication
Take the following 10 day treatment
1) PPI 1 tablet 2x/d for 10 d and
2) Amoxicillin 1 g twice a day for 5 d (day 1-5)
Followed by
3) Clarithromycin 500 mg 2x/d (day 6-10) and
4) Metronidazole 500 mg 2x/d (day 6-10)

DDx of Dyspepsia
Pulmonary
• COPD
• Asthma
• Restrictive lung disease
• Pneumothorax
• Congenital lung disease
• PE

Cardiac
• CHF
• CAD
• MI (recent or past)
• Cardiomyopathy
• Valve dysfunction
• Pericarditis
• Arrhythmia
• Hypertrophy

Mixed/Other
• Deconditioning
• Trauma
• Pain
• Neuromuscular
• Metabolic condition
• Functional: anxiety, panic attack, hyperventilation
Investigations
- CXR, ECG
- PFTs, ABG acutely if indicated

Management
- ABCs: send to ED if in severe respiratory distress
- depends on cause

Dysuria
- see Urology, U10

Definition
- the sensation of pain, burning, or discomfort on urination

Epidemiology
- in adulthood, more common in women than men
- approximately 25% of women report one episode of acute dysuria per year
- most common in women age 25-54 and in those who are sexually active
- in men, dysuria becomes more prevalent with increasing age

Etiology
- infectious
  - most common cause
    - presents as cystitis, urethritis, pyelonephritis, vaginitis, cervicitis, epididymo-orchitis, or prostatitis
- non-infectious
  - hormonal conditions (hypoestrogenism), obstruction (BPH, urethral strictures), allergic reactions, radiation, drugs/chemicals, foreign bodies, trauma, neoplasm, kidney stones, inflammatory diseases, endometriosis, psychogenic

<table>
<thead>
<tr>
<th>Infection</th>
<th>Etiology</th>
<th>Signs and Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>UTI/Cystitis</td>
<td>K. pneumonia, E. coli, Enterobacter, Proteus mirabilis, S. saprophyticus</td>
<td>Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)</td>
</tr>
<tr>
<td>Urethritis</td>
<td>C. trachomatis, N. gonorrhoeae, Trichomonas, Candida, herpes</td>
<td>Internal dysuria throughout micturition, frequency, urgency, incontinence, hematuria, nocturia, back pain, suprapubic discomfort, low grade fever (rare)</td>
</tr>
<tr>
<td>Vaginitis</td>
<td>C. trachomatis, N. gonorrhoeae, Trichomonas, Candida, herpes</td>
<td>External dysuria/pain, vaginal discharge, irritation, dyspareunia, abnormal vaginal bleeding</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>E. coli, C. trachomatis, S. saprophyticus, Proteus mirabilis, Enterobacter, K. pneumoniae</td>
<td>Dysuria, fever, chills, urgency, frequency, tender prostate, rectal pain</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>E. coli, S. saprophyticus, Proteus mirabilis, Enterobacter, K. pneumoniae</td>
<td>Internal dysuria, fever, chills, flank pain radiating to groin, CVA tenderness, NV</td>
</tr>
</tbody>
</table>

Investigations
- no investigations necessary when history and physical consistent with uncomplicated UTI – treat empirically (urinalysis can be performed when indicated by dipstick or microscopy)
- urinalysis/dipstick: positive for nitrites and leukocytes
- urine R&M: pyuria, bacteriuria, hematuria
- urine C&S
- CBC and differential if suspecting pyelonephritis
- if vaginal/urethral discharge present: wet mount, Gram stain, KOH test, vaginal pH, culture for yeast and trichomonas, endocervical/urethral swab or urine PCR for N. gonorrhoeae and C. trachomatis
- radiologic studies and other diagnostic tests if atypical presentation
- see Pediatrics, P63 for UTI in children

Management
- UTI/cystitis
  - pregnant women with bacteriuria (2-7%) must be treated even if asymptomatic, due to increased risk of pyelonephritis, preterm labour, low birth weight and perinatal mortality; need to follow with monthly urine cultures and retreat if still infected
  - patients with recurrent UTIs (>3/yr) should be considered for prophylactic antibiotics
  - if complicated UTI, patients require longer courses of broader spectrum antibiotics
  - urethritis
    - when swab or PCR is positive for chlamydia or gonorrhea must report to Public Health
    - all patients should return 4-7 d after completion of therapy for clinical evaluation

Prevention of UTIs
- Maintain good hydration (especially with cranberry juice) (recommendation level I)
- Wipe urethra from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse

Cranberries for Preventing Urinary Tract Infections
- Cochrane DB Syst Rev 2008;1:CD00121
- Study: Meta-analysis of 10 RCTs (n=1,049).
- Patients: All populations.
- Intervention: Cranberry juice vs. placebo, juice or water was evaluated in seven studies, and cranberry tablets vs. placebo in four studies.
- Main Outcome: UTIs – symptomatic and asymptomatic.
- Results: Cranberry products significantly reduced the incidence of UTIs at 12 mo (RR 0.65, 95% CI 0.46-0.90) compared with placebo/control.
- Conclusion: There is some evidence that cranberry products may decrease the number of symptomatic UTIs over a 12 mo period, particularly for women with recurrent UTIs.
Epistaxis
• see Otolaryngology, OT27

Erectile Dysfunction
• see Urology, U30

Definition
• consistent or recurrent inability to attain and/or maintain penile erection sufficient for sexual performance of ≥3 mo duration

Epidemiology
• ~20% of men age 40; ~50% of men age 70

Etiology
• organic: vascular (90%) (arterial insufficiency, atherosclerosis), endocrine (low testosterone, DM), anatomic (structural abnormality, e.g. Peyronie's), neurologic (post-operative, DM), medications (clonidine, antihypertensives, psychotropics)
• psychogenic (10%)  

Table 18. Differentiation Between Organic and Psychogenic ED

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Organic</th>
<th>Psychogenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>Acute</td>
</tr>
<tr>
<td>Circumstances</td>
<td>Global</td>
<td>Situational</td>
</tr>
<tr>
<td>Course</td>
<td>Constant</td>
<td>Varying</td>
</tr>
<tr>
<td>Non-Coital Erection</td>
<td>Poor</td>
<td>Rigid</td>
</tr>
<tr>
<td>Morning Erection</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Psychossexual Problem</td>
<td>Secondary</td>
<td>Long history</td>
</tr>
<tr>
<td>Partner Problem</td>
<td>Secondary</td>
<td>At onset</td>
</tr>
<tr>
<td>Anxiety and Fear</td>
<td>Secondary</td>
<td>Primary</td>
</tr>
</tbody>
</table>

Walsh: Campbell's Urology, 8th ed. Table 46-4

History
• comprehensive sexual, medical, and psychosocial history
• time course
  • last satisfactory erection
  • gradual or sudden onset
  • attempts at sexual activity
• quantify
  • presence of morning or night time erections
  • stiffness (scale of 1-10)
  • ability to initiate and maintain an erection with sexual stimulation
  • erection stiffness during sex (scale of 1-10)
• qualify
  • partner or situation specific
  • loss of erection before penetration or climax
  • degree of concentration required to maintain an erection
  • percentage of sexual attempts satisfactory to patient and/or his partner
  • significant bends in penis or pain with erection
  • difficulty with specific positions
  • impact on quality of life and relationship

Investigations
• hypothalamic-pituitary-gonadal axis evaluation: testosterone (free + total), prolactin, LH
• risk factor evaluation: fasting glucose, HbA1c, lipid profile
• others: TSH, CBC, urinalysis
• specialized testing
  • psychological and/or psychiatric consultation
  • in-depth psychosexual and relationship evaluation
  • nocturnal penile tumescence and rigidity (NPTR) assessment
  • vascular diagnostics (e.g. doppler studies, angiography)

DDx of Erectile Dysfunction

PENIS
Psychogenic
Endocrine (type 2 DM, testosterone)
Neurogenic (type 2 DM, post-operative)
Insufficiency of blood (atherosclerosis)
Substances

The Effect of Lifestyle Modification and Cardiovascular Risk Factor Reduction on Erectile Dysfunction
Arch Intern Med 2011;171:1797-1803
Study: Meta-analysis of 6 RCTs.
Population: 740 male participants.
Intervention: Lifestyle modification and pharmacotherapy targeting CAD risk factors.
Main Outcome Measure: International Index of Erectile Dysfunction (IIEF-5) score.
Results: Lifestyle modifications and pharmacotherapy for cardiovascular risk factors had a statistically significant association with improved sexual function (weighted mean difference 2.66; 95% CI 1.86-3.47). Lifestyle modification without use of statins was also statistically significantly associated with improved sexual function (weighted mean difference 2.40; 95% CI 1.19-3.61).
Conclusion: Lifestyle modification alone or combined with pharmacotherapy can improve sexual function.

Reasons for Referral to Urology
• Significant penile anatomic disease
• Younger patient with a history of pelvic or perineal trauma
• Cases requiring vascular or neurosurgical intervention
• Complicated endocrinopathies
• Complicated psychiatric or psychosocial problems
• Patient or physician desire for further evaluation
Management

Table 19. Management of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Nonpharmacologic</th>
<th>Pharmacologic</th>
<th>Surgical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes</td>
<td>Oral agents</td>
<td>Implants</td>
</tr>
<tr>
<td>(alcohol, smoking, exercise)</td>
<td>Suppository</td>
<td>Vascular repair</td>
</tr>
<tr>
<td>Relationship/sexual counselling</td>
<td>Male urethral suppository for erection (MUSE)</td>
<td>Realignment</td>
</tr>
<tr>
<td>Vacuum devices</td>
<td>Injections</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- pharmacologic treatment
  - phosphodiesterase type 5 inhibitors
  - α-adrenergic blockers (e.g. yohimbine)
  - serotonin antagonist and reuptake inhibitor (e.g. trazodone)
  - testosterone – currently only indicated in patients presenting with hypogonadism and testosterone deficiency (note: breast/prostate cancer are absolute contraindications)

Table 20. Phosphodiesterase Type 5 Inhibitors

<table>
<thead>
<tr>
<th>Examples</th>
<th>Dosing (1 dose/d)</th>
<th>Specifics</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil (Viagra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>25-100 mg/dose</td>
<td>Take 0.5-4 h prior to intercourse May last 24 h</td>
<td>Flushing, headache, indigestion</td>
<td>Not to be used in patients taking nitrates</td>
</tr>
<tr>
<td>tadalafil (Cialis&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>5-20 mg/dose</td>
<td>Effects may last 36 h</td>
<td>As above</td>
<td>As above</td>
</tr>
<tr>
<td>vardenafil (Levitra&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>2.5-20 mg/dose</td>
<td>Take 1 h prior to intercourse</td>
<td>As above</td>
<td>As above</td>
</tr>
</tbody>
</table>

Fatigue

Epidemiology
- 25% of office visits to family physicians
  - peaks in ages 20-40
  - F:M = 3–4:1
- 50% have associated psychological complaints/problems, especially if <6 mo duration

Differential Diagnosis

Table 21. Differential Diagnosis of Fatigue: PS VINDICATE

| P | Psychogenic          | Depression, life stresses, anxiety disorder, chronic fatigue syndrome, fibromyalgia |
|   | Physiologic          | Pregnancy, caregiving demands (young children, elderly) |
| S | Sleep disturbance    | Obstructive sleep apnea, sleep disorder, poor sleep hygiene, BPH, shift work, pain |
|   | Sedentary            | Unhealthy/sedentary lifestyle |
| V | Vascular             | Stroke |
| I | Infectious           | Viral (e.g. mononucleosis, hepatitis, HIV), bacterial (e.g. TB), fungal, parasitic |
| N | Neoplastic           | Any malignancy |
|   | Nutrition            | Anemia (Fe<sup>2+</sup> deficiency, B<sub>12</sub> deficiency) |
|   | Neurogenic           | Myasthenia gravis, multiple sclerosis, Parkinson’s disease |
| D | Drugs                | β-blockers, antihistamines, anticholinergics, benzodiazepines, antiepileptics, antidepressants |
| I | Idiopathic           | |
| C | Chronic illnesses    | CHF, lung diseases (e.g. COPD, sarcoidosis), renal failure, chronic liver disease |
| A | Autoimmune           | SLE, RA, mixed connective tissue disease, polymyalgia rheumatica |
| T | Toxin                | Substance abuse (e.g. alcohol), heavy metal |
| E | Endocrine            | Hypothyroidism, DM, Cushing’s syndrome, adrenal insufficiency, pregnancy |

Common causes are in bold

Investigations
- psychosocial causes are common, so usually minimal investigation is warranted
- physical causes of fatigue usually have associated symptoms/signs that can be elicited from a focused history and physical exam
- investigations should be guided by history and physical exam and may include
  - CBC and differential, electrolytes, BUN, Cr, ESR, glucose, TSH, ferritin, vit B<sub>12</sub>, serum protein electrophoresis, Bence-Jones protein, albumin, AST, ALT, ALP, bilirubin, calcium, phosphate, ANA, β-hCG
  - urinalysis, CXR, ECG
  - additional tests: serologies (Lyme disease, hepatitis B and C screen, HIV, ANA) and Mantoux skin tests

Fatigue Red Flags
- Fever
- Weight loss
- Night sweats
- Neurological deficits
- Ill-appearing
Treatment
- treat underlying cause
- if etiology cannot be identified (1/3 of patients)
  - reassurance and follow-up, especially with fatigue of psychogenic etiology
  - quick follow-up for reassurance
  - supportive counselling, behavioural, or group therapy
  - encourage patient to stay physically active to maximize function
  - review all medications, OTC, and herbal remedies for drug-drug interactions and side effects
- prognosis: after 1 yr, 40% are no longer fatigued

CHRONIC FATIGUE SYNDROME

Definition (CDC 2006) – must meet both criteria
1. new or definite onset of unexplained, clinically evaluated, persistent or relapsing chronic fatigue, not relieved by rest, which results in occupational, educational, social, or personal dysfunction
2. concurrent presence of ≥4 of the following symptoms for a minimum of 6 mo
  - impairment of short-term memory or concentration, severe enough to cause significant decline in function
  - sore throat
  - tender cervical or axillary lymph nodes
  - muscle pain
  - multi-joint pain with no swelling or redness
  - new headache
  - unrefreshing sleep
  - post-exertion malaise lasting >24 h
- exclusion criteria: medical conditions that may explain the fatigue, certain psychiatric disorders (depression with psychotic or melancholic features, schizophrenia, eating disorders), substance abuse, severe obesity (BMI >45)

Epidemiology
- F>M, Caucasians > other groups, majority in their 30s
- found in <5% of patients presenting with fatigue

Etiology
- unknown, likely multifactorial
- may include infectious agents, immunological factors, neurohormonal factors, and/or nutritional deficiency

Investigations
- no specific diagnostic laboratory tests

Treatment
- promote sleep hygiene
- provide support and reassurance that most patients improve over time
- non-pharmacological
  - regular physical activity, optimal diet, psychotherapy (e.g. CBT), family therapy, support groups
- pharmacological
  - to relieve symptoms: e.g. antidepressants, anxiolytics, NSAIDs, antimicrobials, antiallergy therapy, antihypotensive therapy

Fever
- see Pediatrics, P53

Definition
- oral temperature >37.2°C (AM), 37.7°C (PM)
- fever in children under 2 must be a rectal temperature for accuracy
- TM not accurate for measurement until child is >5 yr
Table 22. Differential Diagnosis of Fever

<table>
<thead>
<tr>
<th>Infection</th>
<th>Cancer</th>
<th>Medications</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial</td>
<td>Leukemia</td>
<td>Allopurinol</td>
<td>Irritable Bowel Syndrome</td>
</tr>
<tr>
<td>Viral TB</td>
<td>Lymphoma</td>
<td>Captopril</td>
<td>Collagen Vascular Disease</td>
</tr>
<tr>
<td></td>
<td>Other Malignancies</td>
<td>Cimetidine</td>
<td>DVT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Heparin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>INH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Meperidine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nifedipine</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenytoin</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Diuretics</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Barbiturates</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antihistamines</td>
<td></td>
</tr>
</tbody>
</table>

History

- fever
  - peak temperature, thermometer, route, duration
  - time of day
  - response to antipyretics
- systemic symptoms
  - weight loss, fatigue, rash, arthralgia, night sweats
- symptoms of possible source
  - UTI/pyelonephritis: dysuria, foul-smelling urine, incontinence, frequency, hematuria, flank pain
  - pneumonia: cough, pleuritic chest pain
  - URTI: cough, coryza, ear pain
  - meningitis: headache, confusion, stiff neck, rash
  - osteomyelitis: bone pain
  - skin: purulent discharge
  - PID: discharge, dyspareunia, lower abdominal pain
  - gastroenteritis: abdominal pain, diarrhea, blood per rectum, vomit
  - medications
  - PE/DVT: swollen legs, pain in calf, SOB, pleuritic chest pain
  - history of cancer/family history of cancer
- infectious contacts
  - travel history, camping, day care, contact with TB, foodborne, animals

Possible Investigations

- CBC and differential, blood culture, urine culture, urinalysis
- stool O&P, Gram stain, culture
- CXR, Mantoux skin test, sputum culture
- LP

Management

- increase fluid intake
- general: sponge bath, light clothing
- acetaminophen/ibuprofen as needed
- treat underlying cause

Headache

- see Neurology, N45

Primary Headaches

Table 23. Primary Headaches

<table>
<thead>
<tr>
<th>Migraine</th>
<th>Tension-Type</th>
<th>Cluster</th>
<th>Caffeine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td></td>
<td>&lt;0.1% of adults, M&gt;&gt;F</td>
<td>~50% of people drinking &gt;2.5 cups/d</td>
</tr>
<tr>
<td>Duration</td>
<td>5-72 h</td>
<td>&lt;3 h at same time of day</td>
<td>Begins 12-24 h after last caffeine intake, can last ~1 wk</td>
</tr>
<tr>
<td>Pain</td>
<td>Classically unilateral and pulsatile, but 40% are bilateral, moderate-severe intensity, N/V, photo-/phonophobia</td>
<td>Mild to moderate pain, bilateral, fronto-occipital or generalized pain, band-like pain, ± contracted neck/ scalp muscles, associated with little disability</td>
<td>Severe, throbbing, associated with drowsiness, anxiety, muscle stiffness, nausea, waves of hot or cold sensations</td>
</tr>
</tbody>
</table>

Migraine Screen

POUND
Pulsatile quality
Over 4-72 h
Unilateral
Nausea and vomiting
Disabling intensity
if ≥4 present then a diagnosis is likely (+LR = 24)
Table 23. Primary Headaches (continued)

<table>
<thead>
<tr>
<th>Triggers</th>
<th>Tension-Type</th>
<th>Cluster</th>
<th>Caffeine Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Migraine</td>
<td>Numerous (e.g. food, sleep</td>
<td>Stressful events, NOT</td>
<td>Often alcohol</td>
</tr>
<tr>
<td></td>
<td>disturbance, stress,</td>
<td>aggravated by physical</td>
<td>Discontinuing</td>
</tr>
<tr>
<td></td>
<td>hormonal, fatigue, weather,</td>
<td>activity</td>
<td>caffeine</td>
</tr>
<tr>
<td></td>
<td>high-altitude)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aggravated by physical</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment of Acute</td>
<td>1st line: acetaminophen,</td>
<td>Rest and relaxation</td>
<td>Sumatriptan</td>
</tr>
<tr>
<td>Headache</td>
<td>NSAIDs, ASA ± caffeine</td>
<td></td>
<td>Caffeine</td>
</tr>
<tr>
<td></td>
<td>2nd line: NSAIDs</td>
<td></td>
<td>Acetaminophen or</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ASA ± caffeine</td>
</tr>
<tr>
<td></td>
<td>3rd line: 5-HT agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>± antiemetic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prophylactic Therapy</td>
<td>1st line: β-blockers</td>
<td>Rest and relaxation,</td>
<td>Lithium carbonate,</td>
</tr>
<tr>
<td></td>
<td>2nd line: TCAs</td>
<td>physical activity,</td>
<td>prednisone, methys</td>
</tr>
<tr>
<td></td>
<td>3rd line: anticonvulsants</td>
<td>biofeedback</td>
<td>seride</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Secondary Headaches
- caused by underlying organic disease
- account for <10% of all headaches, may be life-threatening

Etiology
- aneurysm
- medication overuse headache
- space-occupying lesion
- systemic infection (meningitis, encephalitis)
- stroke
- subarachnoid hemorrhage
- systemic disorders (thyroid disease, HTN, pheochromocytoma, etc.)
- temporal arteritis
- traumatic head injuries
- TMJ or C-spine pathology
- serious ophthalmological and otolaryngological causes of headache

Investigations
- indicated only when red flags are present and may include:
  - CBC for suspected systemic or intracranial infection
  - ESR for suspected temporal arteritis
  - neuroimaging (CT or MRI) to rule out intracranial pathology
  - CSF analysis for suspected intracranial hemorrhage, infection

Management
- based on underlying disorder
- analgesics may provide symptomatic relief

Hearing Impairment
- see Otolaryngology, OT9

Definition
- hearing impairment: a raised hearing threshold measured as decibels of hearing loss relative to the normal population at specific frequencies
- hearing disability: hearing impairment that interferes with performing daily tasks

Epidemiology
- prevalence increases with age (6% of 35-44 yr old, 43% of 65-84 yr old)
- 90% of age-related hearing loss (presbycusis) is sensorineural
- hearing loss detectable by audiology is present in greater than 1/3 of people >65 yr
- associated with significant physical, functional, and mental health consequences

Classification
- conductive (external sound does not reach the middle ear)
- sensorineural involving the inner ear, cochlea, or auditory nerve
- mixed

Assessment
- infants
  - universal newborn hearing screening program

Acupuncture for Migraine Prophylaxis
- Cochrane DB Syst Rev 2006;4:CD001218
- Study: Meta-analysis of 22 RCTs.
- Population: 4,419 participants with diagnosed migraine.
- Intervention: Preventive treatment with acupuncture, sham acupuncture, no prophylactic treatment/routine care only, other interventions.
- Main Outcome Measure: Proportion of responders in 3-4 mo.
- Other Outcomes: Frequency of migraine attacks, number of migraine days, headache frequency.
- Results: Patients receiving acupuncture had higher response rates and fewer headaches after 3-4 mo than those with no prophylactic treatment or routine care only. There was no statistically significant difference between "true" vs. "sham" acupuncture.
- Conclusion: Acupuncture is a viable prophylactic treatment option for migraine attacks. Selecting specific points for acupuncture is not as important as believed by practitioners.

Does this Patient have Hearing Impairment?
- JAMA 2006;295:416-428
- Purpose: To evaluate bedside clinical maneuvers used to evaluate the presence of hearing impairment.
- Study: Evidence-based review of studies examining the accuracy or precision of screening questions and tests. 21 studies were included in this analysis.
- Conclusions: Elderly patients who admit to having hearing impairment should be offered audiometry, while those who do not should undergo a whispered-voice test. Those who hear the whispered voice require no further testing, while those who do not require audiometry. The Weber and Rinne tests are not useful in screening for hearing impairment.
• elderly
  • presbycusis is characterized by the progressive, symmetric loss of high-frequency hearing
    • tinnitus, vertigo, and disequilibrium may be present
    • can cause low self-esteem, isolation, and depression
  • whispered-voice test
    • whisper 6 test words 6 in-2 ft away from the patient's ear out of the visual field, ask
      patient to repeat the words (with non-test ear distraction)
  • tuning fork test (to distinguish conductive from sensorineural hearing loss)
    • Rinne and Weber (not for general screening)
  • formal audiologic assessment
    • pure tone, air, and bone conduction testing
    • speech audiometry
    • impedance audiometry

Management
• counsel about noise control and hearing protection programs (Grade A evidence)
• investigations in patients with unexplained sensorineural hearing loss
  • blood sugar, CBC+ differential, TSH, syphilis testing
• referral
  • refer patients with hearing loss for a complete audiological examination
  • unclear etiology of hearing loss: referral to ENT
• sudden hearing loss: urgent referral as treatment success is related to early treatment
• patients with progressive asymmetric sensorineural hearing loss should have an MRI/CT scan to
  exclude vestibular schwannoma (acoustic neuroma)
• hearing amplification (e.g. hearing aids), assistive listening devices, and cochlear implants can
  dramatically improve quality of life

Hypertension

Hypertension Guidelines are reviewed and updated annually, for up-to-date recommendations, please see www.hypertension.ca/chep

Epidemiology
• 22% of Canadian adults suffer from HTN (prevalence is 52% in the 60-70 age group)
• lifetime risk of developing hypertension is approximately 90%
• 64% of Canadians who have HTN are treated and controlled, while 17% are unaware that they
  have HTN
• 3rd leading risk factor associated with death
  • risk factor for CAD, CHF, cerebrovascular disease, renal failure, peripheral vascular disease

Definitions
• HTN
  • BP ≥140/90 mmHg, unless DM (≥130/80 mmHg), or age ≥80 yr (≥150/90 mmHg)
• isolated systolic HTN
  • sBP ≥140 and dBP <90
  • associated with progressive reduction in vascular compliance
  • usually begins in 5th decade
• hypertensive urgency
  • sBP >210 or dBP >120 with minimal or no target-organ damage
• hypertensive emergency
  • severe HTN + acute target-organ damage
• accelerated HTN
  • significant recent increase in BP over previous hypertensive levels associated with
    evidence of vascular damage on fundoscopy, but without papilledema
• malignant HTN
  • sufficient elevation in BP to cause papilledema and other manifestations of vascular
    damage (retinal hemorrhages, bulging discs, mental status changes, increasing creatinine)
• white coat hypertension
  • high clinic BP with normal home BP and 24 ambulatory BP, caused by anxiety in clinic
• masked hypertension
  • normal clinic BP with high BP in home and/or ambulatory setting, often provoked by
    anxiety, job stress, exercise

Etiology
• essential (primary) HTN (>90%)
• undetermined cause
• secondary HTN (10%)
Predisposing Factors

- family history
- obesity (especially abdominal)
- alcohol consumption
- stress
- sedentary lifestyle
- smoking
- male
- age >30
- excessive salt intake/fatty diet
- African American ancestry
- dyslipidemia

Table 24. Causes of Secondary HTN

<table>
<thead>
<tr>
<th>Common Cause</th>
<th>Renal Renovascular HTN Renal parenchymal disease, glomerulonephritis, pyelonephritis, polycystic kidney</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal</td>
<td>1º hyperaldosteronism Pheochromocytoma Cushing’s syndrome Hyperthyroidism/hyperparathyroidism Hypercalcemia of any cause</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Coarctation of the aorta Renal artery stenosis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Cocaine Estrogens/OCP MAOIs Lithium Amphetamines NSAIDs Decongestants Alcohol</td>
</tr>
</tbody>
</table>

Investigations

- for all patients with HTN
  - electrolytes, Cr, fasting glucose and/or HbA1c, lipid profile, 12-lead ECG, urinalysis
  - self-measurement of BP at home is encouraged (recommended devices listed at www.hypertension.ca)
- for specific patient subgroups
  - DM or chronic kidney disease: urinary protein excretion
  - if suspected renovascular HTN: renal ultrasound, captopril renal scan (if GFR >60 mL/min), MRA/CTA (if normal renal function)
  - if suspected endocrine cause: plasma aldosterone, plasma renin
    - measured from morning samples taken from patients in sitting position after resting 15 min
    - discontinue aldosterone antagonists, ARBs, β-blockers, and clonidine prior to testing
  - if suspected pheochromocytoma: 24 h urine for metanephrines and creatinine
  - echocardiography for left ventricular dysfunction assessment if indicated

Diagnosis

- all Canadian adults should have BP assessed at all appropriate clinical visits, oscillometric preferred to manual
Figure 11. Assessment of patients with hypertension

Adapted from: CHEP 2015 Guidelines

Treatment
- treat to target BP: <140/90 mmHg, <130/80 mmHg if DM, sBP<150 in very elderly (>80 yrs)
- optimum management of hypertension requires assessment of overall cardiac risk
- lifestyle modification (in all HTN patients)
  - may be sufficient in patients with stage 1 HTN (140-159/90-99)
  - diet
    - follow Canada’s Guide to Healthy Eating (see Nutrition, FM6) and Dietary Approaches to Stop Hypertension (DASH) (reduced cholesterol and saturated fats)
    - limit daily sodium intake to 65-100 mmol (1.5-2.3 g)
    - potassium/magnesium/calcium supplementations are NOT recommended for HTN
    - moderate intensity dynamic exercise: 30-60 min, 4-7 x/wk; higher intensity exercise is no more effective
    - smoking cessation
    - stress management
    - low-risk alcohol consumption (see Alcohol, FM13)
    - achieve and maintain a healthy BMI (18.5-24.9 kg/m²) and waist circumference (<102 cm for men, <88 cm for women); use multidisciplinary approach to weight loss
    - individualized cognitive behavioural interventions for stress management
- pharmacological
  - indications regardless of age (caution with elderly patients)
    - dBP ≥90 mmHg with target organ damage or independent cardiovascular risk factors
    - dBP ≥100 mmHg or sBP ≥160 mmHg without target organ damage or cardiovascular risk factors
    - sBP ≥140 with target organ damage
  - first line antihypertensives: thiazide/thiazide-like diuretic, ACEI (for non-African patients), ARB, long-acting CCB, β-blocker (if age <60)
  - if partial response to standard dose monotherapy, add another first-line drug
  - caution with combination of non-DHP CCB and β-blocker
  - combination of ACEI and ARB is not recommended
  - be cautious of hypokalemia in patients treated with thiazide/thiazide-like diuretic monotherapy
  - if still not controlled or adverse effects, can add other classes of anti-hypertensives
  - focus on adherence to health behavior modification and pharmacotherapy; should be assessed at each visit

Impact of Health Behaviour on Blood Pressure

<table>
<thead>
<tr>
<th>Intervention</th>
<th>SBP (mmHg)</th>
<th>DBP (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and weight control</td>
<td>-6.0</td>
<td>-4.8</td>
</tr>
<tr>
<td>Reduced salt/sodium intake</td>
<td>-5.4</td>
<td>-2.8</td>
</tr>
<tr>
<td>Reduced alcohol intake</td>
<td>-3.4</td>
<td>-3.4</td>
</tr>
<tr>
<td>DASH diet</td>
<td>-11.4</td>
<td>-5.5</td>
</tr>
<tr>
<td>Physical activity therapies</td>
<td>-3.1</td>
<td>-1.8</td>
</tr>
<tr>
<td>Relaxation therapies</td>
<td>-3.7</td>
<td>-3.5</td>
</tr>
</tbody>
</table>


β-blocker
Not recommended as first line for patients of age ≥60

ACEI
Not recommended as monotherapy in people of African descent
### Table 25. Pharmacologic Treatment of Hypertension in Patients with Unique Conditions

<table>
<thead>
<tr>
<th>Condition or Risk Factor</th>
<th>Recommended Drugs</th>
<th>Alternative Drugs</th>
<th>Not Recommended/Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isolated Diastolic HTN</strong></td>
<td>Thiazide diuretic, β-blocker, ACEI, ARB, or long-acting CCB (consider ASA and statin in select patients)</td>
<td>Combinations of first-line drugs</td>
<td>β-blocker monotherapy (age &gt;60) or combination of ACEI with an ARB</td>
</tr>
<tr>
<td><strong>Isolated Systolic HTN</strong></td>
<td>Thiazide diuretic, ARB, or long-acting dihydhydropyridine CCB</td>
<td>Combinations of first-line drugs</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>CAD</strong></td>
<td>ACEI or ARB; β-blocker for patients with stable angina</td>
<td>Long acting CCB, when combination therapy for high risk patients, ACEI/DHP CCB is preferred</td>
<td>Short-acting CCB (nifedipine) or ACEI + ARB is not recommended if dBP 60 mmHg may exacerbate MI</td>
</tr>
<tr>
<td><strong>Prior MI</strong></td>
<td>β-blocker + ACEI (ARB if cannot tolerate ACEI)</td>
<td>Long-acting CCB</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td><strong>Left Ventricular Hypertrophy</strong></td>
<td>ACEI, ARB, thiazide, or long-acting CCB</td>
<td>Combination of additional agents</td>
<td>Hydralazine and minoxidil can increase LVH, thus not recommended</td>
</tr>
<tr>
<td><strong>Cerebrovascular Disease</strong></td>
<td>ACEI + diuretic</td>
<td>Combination of additional agents</td>
<td>ACEI + ARB combination after a stroke is not recommended</td>
</tr>
<tr>
<td><strong>Heart Failure</strong></td>
<td>ACEI (ARB if ACEI intolerant) and β-blocker</td>
<td>ARB in addition to ACEI</td>
<td>Non-DHP CCB not recommended</td>
</tr>
<tr>
<td><strong>Dyslipidemias</strong></td>
<td>Thiazide diuretic, β-blocker, ACEI, or long-acting CCB</td>
<td>Hydralazine and minoxidil can increase LVH, thus not recommended</td>
<td></td>
</tr>
<tr>
<td><strong>DM with Albuminuria</strong></td>
<td>ACEI or ARB (DHP CCB &gt; HCTZ for combination therapy with ACEI)</td>
<td>Add thiazide diuretic, cardioselective β-blocker, long acting CCB</td>
<td>If serum Cr &gt;150 μmol/L, a loop diuretic should be considered instead of low-dose thiazide diuretic</td>
</tr>
<tr>
<td><strong>DN without Albuminuria</strong></td>
<td>ACEI, ARB, DHP CCB, or thiazide diuretic</td>
<td>Combination of first-line drugs or, first-line agents not tolerated, cardioselective β-blocker or non-DHP CCB</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td><strong>Non-Diabetic Chronic Kidney Disease with Proteinuria</strong></td>
<td>ACEI (ARB if ACEI intolerant), diuretic as additive therapy</td>
<td>Thiazide for additive antihypertensive therapy, loop diuretic for volume overload</td>
<td>ACEI + ARB combination is not recommended</td>
</tr>
<tr>
<td><strong>Renovascular Disease</strong></td>
<td>Same as HTN without other indications</td>
<td>Caution in using ACEI or ARB – monitor for AKI</td>
<td>Renal angioplasty and stenting offer no benefits over optimal medical therapy alone</td>
</tr>
<tr>
<td><strong>Asthma</strong></td>
<td>K+-sparing + thiazide diuretic for patients on salbutamol</td>
<td>β-blocker, unless specific indications like angina or post-MI</td>
<td>Caution with use of ASA in patients with uncontrolled BP</td>
</tr>
<tr>
<td><strong>Gout</strong></td>
<td>Low dose thiazide ACEI</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Smoking</strong></td>
<td>Hydralazine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pregnancy</strong></td>
<td>Methyldopa</td>
<td>Labetalol</td>
<td>ACEI</td>
</tr>
<tr>
<td><strong>Elderly (&gt;60 yr)</strong></td>
<td>As for uncomplicated isolated diastolic HTN, except for use of β-blocker</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Emergency</strong></td>
<td>BP &gt; 169/90 = labetalol, nifedipine</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>If &gt;3 Cardiovascular Risk Factors or Established Atherosclerotic Disease</strong></td>
<td>Statin (age &gt;40), low-dose ASA (age &gt;50)</td>
<td>Caution with use of ASA in patients with uncontrolled BP</td>
<td></td>
</tr>
</tbody>
</table>

**Thiazides as First-Line Antihypertensive Therapy – ALLHAT**

**Study:** Randomized, double-blind, active-controlled clinical trial with mean follow-up of 4.9 yr.
**Patients:** 33,957 participants (mean age 67 yr, 52% male, 47% white) with stage 1 or 2 HTN and at least one other CHD risk factor.
**Intervention:** Participants were randomly assigned to receive chlorthalidone (12.5-25 mg/d), amlodipine (2.5-10mg/d), or lisinopril (10-40 mg/d). Target BP was <140/90 mmHg, achieved by titrating the assigned study drug, and adding open-label agents when necessary.
**Outcomes:** The primary outcome was combined fatal CHD or non-fatal MI. Secondary outcomes were all-cause mortality, stroke, combined CHD, and combined CVD.
**Results:** There were no significant differences in either the primary outcome or all-cause mortality between treatment groups. For amlodipine vs. chlorthalidone, secondary outcomes were similar except for a higher 6 yr rate of heart failure with amlodipine (10.2% vs. 7.7%; p<0.001). For lisinopril vs. chlorthalidone, lisinopril had higher 6 yr rates of combined CVD (33.3% vs. 30.9%; p<0.001), stroke (6.3% vs. 5.0%; p<0.002) and heart failure (6.7% vs. 7.7%; p<0.001).
**Conclusion:** Thiazide-type diuretics are superior to CCB and ACEI for preventing one or more major forms of CVD, with similar risks of death and non-fatal MI.

### Table 25. Pharmacologic Treatment of Hypertension (in general)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommended Drugs</th>
<th>Alternative Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ACEI</td>
<td>CCB</td>
</tr>
<tr>
<td></td>
<td>β-blocker</td>
<td>Diuretic</td>
</tr>
</tbody>
</table>

**Calcium Channel Blockers**

- Dihydropyridine CCBs
  - amlodipine
  - felodipine
  - nifedipine

- Non-Dihydropyridine CCBs
  - diltiazem
  - verapamil

**How to Combine Antihypertensive Medications**

- ACEI
- β-blocker
- CCB
- Diuretic

**Adapted from:** McAliney FA, Zamka KB, Campbell NRC, et al. The 2001 Canadian recommendations for the management of hypertension: Part two – Therapy. Can J Cardiol 2002;18:629-641 and The 2012 Canadian Hypertension Education Program Recommendations
Follow-Up
- assess and encourage adherence to pharmacological and non-pharmacological therapy at every visit
- lifestyle modification → q3-6mo
- pharmacological
  - q1-2mo until BP under target for 2 consecutive visits
  - more often for symptomatic HTN, severe HTN, antihypertensive drug intolerance, target organ damage
  - q3-6mo once at target BP
- referral is indicated for cases of refractory HTN, suspected secondary cause or worsening renal failure
- hospitalization is indicated for malignant HTN

Joint Pain
- see Rheumatology, RH3

Table 26. Differential Diagnosis of Joint Pain

<table>
<thead>
<tr>
<th>Localized</th>
<th>Generalized</th>
<th>Inflammatory</th>
<th>Articular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Articular</td>
<td>Generalized</td>
<td>Inflammatory</td>
<td>Articular</td>
</tr>
<tr>
<td>• Buritis • Tendinitis • Capsulitis</td>
<td>• Fibromyalgia • Polymyalgia rheumatica • Myofascial pain syndrome</td>
<td>Seropositive</td>
<td>Seronegative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• RA • Systemic lupus erythematosus • Scleroderma</td>
<td>• Ankylosing spondylitis • Inflammatory bowel disease • Psoriatic arthritis • Reactive arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Polymyositis/Dermatomyositis</td>
<td>• Rheumatoid arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Sjögren’s syndrome</td>
<td>• Reactive arthritis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Crystal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Gout • Psuedogout • Hydroxyapatite</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Infectious/septic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Gonococcal • Non-gonococcal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Systemic vasculitis disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History
- number of joints involved: monoarticular, oligoarticular, polyarticular
- pattern of joints involved: symmetrical vs. asymmetrical, large vs. small joints, axial skeleton
- onset: acute vs. chronic (>6 wk)
- trauma, infection, medications (steroids, diuretics)
- morning stiffness (duration) vs. worse at end of day
- FHx of arthritis
- comorbidities: DM (carpal tunnel syndrome), renal insufficiency (gout), psoriasis (psoriatic arthritis), myeloma (low back pain), osteoporosis (fracture), obesity (OA)
- constitutional symptoms (neoplasm)

Physical Exam
- vitals
- specific joint exams
- systemic features (skin, nails, eyes, hands)

Investigations (Guided by the History and Physical Exam)
- general: CBC and differential, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen
- complement (C3, C4)
- urinalysis to detect disease complications (proteinuria, active sediment)
- serology (ANA, anti-dsDNA, HLA-B27, anti-Jo-1, anti-Sm, anti-La, anti-Ro, RhF, and anti-CCP, etc.)
- synovial fluid analysis (cell count + differential, culture, Gram stain, microscopy)
- tissue cultures
- radiology (plain film, CT, MRI, U/S, bone densitometry, angiography, bone scan)

Signs and Symptoms of Inflammatory Arthritis
- WARM(S) Joints
  - Worse with rest, better with activity
  - Awakening in the latter half of the night
  - Redness around joint
  - Morning stiffness (>30 min)
  - Soft tissue swelling, erythema
Treatment

- patient education including lifestyle modifications
- physiotherapy, occupational therapy
- manage pain (acetaminophen, NSAIDs)
- treat specific causes (e.g. antibiotics, DMARDs etc., see Rheumatology, RH30)

Low Back Pain

- see Orthopedics, OR24

Definition

- acute: <6 wk
- subacute: 6-12 wk
- chronic: >12 wk

Epidemiology

- 5th most common reason for visiting a physician
- lifetime prevalence: 90%
- peak prevalence: age 45-60
- largest WSIB category
- most common cause of chronic disability for individuals <45 yr old
- 90% resolve in 6 wk, <5% become chronic

Etiology

- source of pain can be local, radicular, referred, or related to a psychiatric illness
- 98% are mechanical causes
  - pain is worse with movement, better with rest
  - sprain (ligament), strain (muscle), facet joint degeneration, disc degeneration/herniation, spinal stenosis (e.g. spondylosis), spondylolisthesis, compression fracture, pregnancy
- 2% are non-mechanical causes
  - surgical emergencies
  - cauda equina syndrome (areflexia, lower extremity weakness, decreased anal tone, saddle anesthesia, fecal incontinence, urinary retention), AAA (pulsatile abdominal mass)
  - medical conditions
    - neoplastic (primary, metastatic, multiple myeloma)
    - infectious (osteomyelitis, TB)
    - metabolic (osteoporosis, osteomalacia, Paget’s disease)
    - rheumatologic (ankylosing spondylitis, polymyalgia rheumatica)
    - referred pain (perforated ulcer, pancreatitis, pyelonephritis, ectopic pregnancy, herpes zoster)

Physical Exam

- inspection: curvature, posture, gait
- palpation: bony deformities/tenderness, paraspinal muscle bulk/tenderness, trigger points
  - percussion of spine to elicit pain due to fracture or infection
- ROM and peripheral pulses
- neurologic exam for L4/L5/S1 helps determine level of spinal involvement (power, reflexes, sensation)
- special tests
  - straight leg raise (positive if pain at <70 degrees and aggravated by ankle dorsiflexion), positive test is indicative of sciatica
  - crossed straight leg raise (raising of uninvolved leg elicits pain in leg with sciatica), more specific than straight leg raise
  - femoral stretch test (patient prone, knee flexed, examiner extends hip) to diagnose L4 radiculopathy

Investigations

- plain films not recommended in initial evaluation
- if infection/cancer suspected: CBC, ESR
- if neurologic deficits worsening or infection/cancer suspected: consider CT or MRI
A Summary of the Guideline for the Evidence-Informed Primary Care Management of Low Back Pain

**Red Flags** help identify rare, but potentially serious conditions. They include:
- Features of Cauda Equina Syndrome including sudden onset of loss of bladder/bowel control, saddle anesthesia (EMERGENCY)
- Severe worsening pain, especially at night or when lying down (URGENT)
- Significant trauma (URGENT)
- Weight loss, history of cancer, fever (URGENT)
- Use of steroids or intravenous drugs (URGENT)
- Patient with first episode over 50 years old, especially over 80 (SSOON)
- Widespread neurological signs (SSOON)

**EMERGENCY** — referred within hours
**URGENT** — referred within 24 – 48 hours
**SSOON** — referred within weeks

**Yellow Flags** indicate psychosocial barriers to recovery. They include:
- Belief that pain and activity are harmful
- Sickness behaviour* (like extended rest)
- Low or negative mood, social withdrawal
- Treatment expectations that do not fit best practice
- Problems with claim and compensation
- History of back pain, time-off, other claims
- Problems at work, poor job satisfaction
- Heavy work, unachievable hours (shift work)
- Overprotective family or lack of support

---

**Figure 12. Low back pain treatment**


**Table 27. Approach to Non-Traumatic Low Back Pain**

<table>
<thead>
<tr>
<th>Back Dominant</th>
<th>Leg Dominant</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History</strong></td>
<td><strong>Pathology</strong></td>
</tr>
<tr>
<td>Worsen with flexion</td>
<td>Arising from intervertebral discs or adjacent ligaments</td>
</tr>
<tr>
<td>Constant/intermittent</td>
<td>(associated ligaments and capsular structures)</td>
</tr>
<tr>
<td><strong>Physical Exam</strong></td>
<td><strong>Likely Pathology</strong></td>
</tr>
<tr>
<td>Normal neuro exam</td>
<td>Sciatica</td>
</tr>
<tr>
<td>Fast responder</td>
<td>Neurogenic claudication</td>
</tr>
<tr>
<td><strong>Possible</strong> Pathology</td>
<td></td>
</tr>
<tr>
<td>Improves with extension</td>
<td></td>
</tr>
<tr>
<td>Slow responder</td>
<td></td>
</tr>
<tr>
<td><strong>Likely</strong> Pathology</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Management</strong></td>
<td><strong>Neurological findings</strong></td>
</tr>
<tr>
<td>Lumbar roll</td>
<td>Sciatica</td>
</tr>
<tr>
<td>Night lumbar roll</td>
<td>Neurogenic claudication</td>
</tr>
<tr>
<td>Medication as required</td>
<td></td>
</tr>
</tbody>
</table>

---

Menopause/Hormone Replacement Therapy

- see Gynecology, GY34

Epidemiology
- mean age of menopause = 51.4 yr

Clinical Features
- associated with estrogen deprivation
- urogenital tract: atrophy, vaginal dryness/itching, urinary frequency/urgency/incontinence, bleeding
- blood vessels and heart: vasomotor instability (e.g., hot flashes), increased risk of heart disease
- bones: bone loss, joint/muscle/back pain, fractures, loss of height
- brain: depression, irritability, mood swings, memory loss

Management
- encourage physical exercise, smoking cessation, and a balanced diet with adequate intake/supplementation of calcium (1,200-1,500 mg/d) and vitamin D (800-2,000 IU/d)
- hormone replacement therapy (HRT)
  - prescribe for moderate to severe symptoms for no longer than 5 yr; routine use is not recommended
  - regimens: cyclic estrogen-progestin, continuous estrogen-progestin, estrogen only (if no uterus), estrogen patch/gel/cream/ring/vaginal tablet
  - decreases risk of osteoporotic fractures, colorectal cancer
  - increases risk of breast cancer, coronary heart disease, stroke, DVT, and PE
  - initiation of HRT requires a thorough discussion of short- and long-term benefits and risks
- consider venlafaxine, SSRIs, or gabapentin to ease vasomotor instability

Osteoarthritis

- see Rheumatology, RH5

Epidemiology
- most common form of arthritis seen in primary care
- prevalence is 10-12% and increases with age
- results in long-term disability in 2-3% of patients with OA
- almost everyone over the age of 65 shows signs of OA on x-ray, but only 33% of these individuals will be symptomatic

Clinical Features
- joint pain with activity, improved with rest, morning stiffness or gelling <30 min
- deformity, bony enlargement, crepitus, limitation of movement, peri-articular muscle atrophy
- usually affects distal joints of hands, spine, hips, and knees

Investigations
- no laboratory tests for the diagnosis of OA
- hallmark radiographic features: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes

Management
- goals: relieve pain, preserve joint motion and function, prevent further injury
- conservative
  - patient education, weight loss, low-impact exercise (OT/PT), assistive devices (e.g., canes, orthotics, raised toilet seats)
- pharmacological
  - consider comorbidities such as PUD, HTN, IHD, hepatic disease, and renal disease
  - medications do not alter natural course of OA
  - 1st line: acetaminophen up to 4 g/d (OA is not an inflammatory disorder)
  - 2nd line: NSAIDs in the lowest effective dose for the shortest duration of time, along with gastroprotection; COX-2 selective inhibitors (celecoxib/Celebrex®) are recommended if long-term treatment or if high risk for serious GI problems
  - combination analgesics (e.g., acetaminophen and codeine)
  - intra-articular hyaluronic acid injections
  - intra-articular corticosteroid injections (no more than 3-4x/yr) may be helpful in acute flares (benefits last 4-6 wk, can be up to 6 mo)
  - topical NSAID (diclofenac/Pennsaid®)
  - capsaicin cream (Zostrix®)
  - oral glucosamine
  - surgery
  - consider if persistent significant pain and functional impairment despite optimal pharmacotherapy (e.g., debridement, osteotomy, total joint arthroplasty)

Glucosamine Therapy for Treating Osteoarthritis
This meta-analysis of 25 single- and double-blinded randomized controlled trials with 4,863 patients compared glucosamine treatment, administered by any route, against placebo or another treatment.

Conclusions: Glucosamine can decrease pain and functional impairment resulting from OA and is not associated with any side effects compared to placebo. Differences in the effectiveness of Rotta and non-Rotta preparations highlight variability between glucosamine preparations and patients should be made aware of this.
Osteoporosis

- see Endocrinology, E42
- for current guidelines and tools see www.osteoporosis.ca
- age-related disease characterized by decreased bone mass and increased susceptibility to fractures
- affects 1 in 4 Canadian women and 1 in 8 Canadian men

For more information, see the Endocrinology section (E42) and visit the website www.osteoporosis.ca for current guidelines and tools.

Disorders Strongly Associated with Osteoporosis Include:
- Primary hyperparathyroidism, type 1 DM, osteogenesis imperfecta, uncontrolled hyperthyroidism, hypogonadism or premature menopause (<45 yr), Cushing’s disease, chronic malnutrition or malabsorption, chronic liver disease, COPD, and chronic inflammatory conditions (e.g. IBD)

10 Yr Fracture Risk Assessment
- FRAX (WHO Fracture Risk Assessment Tool) and CAROC (Canadian Association of Radiologists and Osteoporosis Canada) have been validated in the Canadian Population
- FRAX and CAROC are available online from: https://www.osteoporosis.ca/

How much Calcium do we Need?

<table>
<thead>
<tr>
<th>Age</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-8</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>9-18</td>
<td>1,300 mg</td>
</tr>
<tr>
<td>19-50</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1,200 mg</td>
</tr>
<tr>
<td>Pregnant and lactating women</td>
<td>1,000 mg</td>
</tr>
<tr>
<td>19-50</td>
<td></td>
</tr>
</tbody>
</table>

Calcium Content of Common Foods

- 1 cup milk = 300 mg
- ½ cup yogurt = 332 mg
- ½ can salmon with bones = 240 mg
- ½ cup cooked broccoli = 33 mg
- 1 medium orange = 50 mg

Vitamin D Content in Food

- Milk fortified with vitamin D3 contains 100 IU's per 250 mL glass
- Foods such as margarine, eggs, chicken livers, salmon, sardines, herring, mackerel, swordfish, and fish oils (halibut and cod liver oils) all contain small amounts; supplementation is necessary to obtain adequate levels as dietary intake has minimal impact
- Most multivitamins provide 400 IU's of vitamin D3

Palliative and End-of-Life Care

- see Geriatric Medicine, GM12

Figure 14. 2010 Clinical practice guidelines for the diagnosis and management of osteoporosis in Canada (integrated management model). Adapted from: CMAJ 2010;182:1864-1873
### Rash

**ATOPIK DERMATITIS**
- **clinical features**
  - affects all ages but is more common in children
  - pruritus is the most common symptom; scratching worsens the rash creating a vicious cycle
- **treatment**
  - goals: limit itching, repair skin
  - moisturizers, emollients, topical corticosteroids; oral corticosteroids and topical calcineurin inhibitors may be used

**SEBORREIC DERMATITIS**
- **clinical features**
  - affects all ages but is most common in infants within the first 3 mo of life (e.g. pityriasis capitis or "cradle cap") and adults age 30-60 yr
  - affects the scalp, central face, and anterior chest; often presents as scalp scaling (dandruff) in adolescents and adults
  - may cause mild to marked erythema of the nasolabial fold, often with greasy scaling
- **treatment**
  - topical antifungals, topical low-potency steroids; topical calcineurin inhibitors may be used

**ROSACEA**
- **clinical features**
  - stages: (1) facial flushing, (2) erythema and/or edema and ocular symptoms, (3) papules and pustules, (4) rhinophyma
- **treatment**
  - topical or oral antibiotics, oral retinoids
  - laser treatment may be an option for progressive telangiectasias or rhinophyma
  - referral may be required to manage rhinophyma, ocular complications, or severe disease

**ACNE VULGARIS**
- **clinical features**
  - types: (I) comedonal, (II) papular, (III) pustular, (IV) nodulocystic
  - predilection for the face, neck, upper chest, and back
- **treatment**
  - mild acne: topical treatments (antibiotics, benzoyl peroxide, retinoids)
  - moderate acne: after topical treatments have failed, add oral antibiotics and consider hormonal therapy
  - severe acne: consider systemic retinoids

**ONYCHOMYCOSIS (TINEA UNGUIUM)**
- **definition**: fungal infection of the nail bed, matrix, or plate
- **clinical features**
  - occurs primarily in adults, most commonly after age 60
  - crumbling, distally dystrophic nails; yellowish, opaque with subungual hyperkeratotic debris
  - toenails are affected more often than fingernails
- **investigations**
  - microscopy of subungual scrapings under KOH preparation, culture
- **treatment**
  - oral antifungals (terbinafine/Lamisil®, itraconazole/Sporanox®), topical antifungals (ciclopirox/Loprox®) are less effective
Sexually Transmitted Infections

- see Gynecology, GY27

**Definition**
- diverse group of infections caused by multiple microbial pathogens
- transmitted by either secretions or fluids from mucosal surfaces

**Epidemiology**
- high incidence rates worldwide
- Canadian prevalence in clinical practice
  - common: chlamydia (most common), gonorrhea (2nd most common), HPV, genital herpes (increasing incidence of chlamydia and gonorrhea)
  - less common: hepatitis B, HIV, and syphilis (increasing in incidence), trichomoniasis
  - rare: chancroid, granuloma inguinale, lymphogranuloma venereum
- non-sexually transmitted genital tract infections: vulvovaginal candidiasis (VVC), bacterial vaginosis (BV)
- three most common infections associated with vaginal discharge in adult women are BV, VVC, and trichomoniasis

**History**
- sexual history
  - age of first intercourse, sexual orientation, sexual activity (oral, anal, and/or vaginal intercourse), sexual activity during travel
  - total number of partners in the past year/month/week and duration of involvement with each
- STI history
  - STI awareness, contraception, previous STIs and testing (including Pap tests), partner communication regarding STIs
  - local symptoms such as burning, itching, discharge, sores, vesicles, testicular pain, dysuria, abdominal pain
  - systemic symptoms such as fever, lymphadenopathy, arthralgia

**Investigations/Screening**
- individuals at increased risk, even those who are asymptomatic, should be screened for chlamydia, gonorrhea, hepatitis B, HIV, and syphilis
- Pap test if none performed in the preceding 12 mo

**Management**
- primary prevention is vastly more effective than treating STIs and their sequelae
- offer hepatitis B vaccine if not immune
- offer Gardasil® to women over 9 years of age (can be offered to men as well but not covered by OHIP)
- discuss STI risk factors (e.g. decreasing the number of sexual partners)
- direct advice to ALWAYS use condoms or to abstain from intercourse
- condoms are not 100% effective against HPV or HSV
- an STI patient is not considered treated until the management of his/her partner(s) is ensured (contact tracing by Public Health)
- patients diagnosed with bacterial STI or trichomonal infection should abstain from sexual activity until treatment completion and for 7 d after treatment for both partners, or until test of cure completed
- mandatory reporting: chlamydia, gonorrhea, hepatitis B, HIV, syphilis

**STI Risk Factors**
- Sexually active males and females
- Unprotected sex, sexual contact with a known case of STI, previous STI
- New sexual partner or > 2 sexual partners in the past 12 mo
- Street involved, homeless, and/or substance abuse

**Efficacy of Human Papillomavirus Vaccines – A Systematic Quantitative Review**
*Int J Gynecol Cancer* 2009;19:1166-1176

**Study:** Systematic review of 6 randomized placebo-controlled double-blind trials.

**Patients:** 47,236 women between ages 9-26.

**Intervention:** Vaccination with HPV L1 virus-like particle in either quadrivalent (HPV 6, 11, 16, 18), bivalent (HPV 16, 18), or univalent (HPV 16) form vs. placebo.

**Main Outcome:** Prevention of cytologically and/or histologically proven lesions (including LSIL, HSIL, VIN, VAIN, AVN, adenocarcinoma in situ of the cervix, or cancer of the cervix associated with HPV infection).

**Results:** Bivalent and quadrivalent vaccines reduced the rate of lesions in the cervix, vulva, vagina, and anogenital region with efficacy of 93% and 62%, respectively.
Sinusitis

- see Otolaryngology, OT25

Etiology
- viral etiology is more common
- viral: rhinovirus, influenza, parainfluenza
- bacterial: S. pneumoniae, H. influenzae, M. catarrhalis

Management of Acute Sinusitis
- may provide symptom relief: oral analgesics (acetaminophen, NSAIDs), nasal saline rinse, short-term use of topical or oral decongestants
- do not prescribe antihistamines
- intra-nasal corticosteroids if diagnosed with mild to moderate acute bacterial sinusitis
- antibiotics and intra-nasal corticosteroids if diagnosed with severe acute bacterial sinusitis
- ENT referral if: anatomic defect (e.g. deviated septum, polyp, adenoid hypertrophy), failure of second-line therapy, ≥4 episodes/yr, development of complications (e.g. mucocele, orbital extension, meningitis, intra-cranial abscess, venous sinus thrombosis)

Red Flags for Urgent Referral
- Altered mental status
- Headache
- Systemic toxicity
- Swelling of the orbit or change in visual acuity or EOM
- Hard neurological findings
- Signs of meningeal irritation
- Suspected intra-cranial complications (meningitis, intra-cranial abscess, cavernous sinus thrombosis)
- Involvement of associated structures (periorbital cellulitis, Pett’s puffy tumour)
Sleep Disorders

- see Respirology, R31 and Neurology, N48

Definition
- most often characterized by one of three complaints
  - insomnia
    - difficulty falling asleep, difficulty maintaining sleep, early-morning wakening, non-refreshing sleep
  - parasomnias
    - night terrors, nightmares, restless leg syndrome, somnambulism (performing complex behaviour during sleep with eyes open but without memory of event)
    - excessive daytime sleepiness

Epidemiology
- 1/3 of patients in primary care setting have occasional sleep problems, 10% have chronic sleep problems
Etiology

- primary sleep disorders
  - primary insomnia, narcolepsy, obstructive sleep apnea, restless leg syndrome, periodic limb movements of sleep
- secondary causes
  - medical: COPD, asthma, CHF, hyperthyroidism, chronic pain, BPH, menopause, GERD, PUD, pregnancy, neurological disorders
  - drugs: alcohol, caffeine, nicotine, nicotine replacement therapy, β-agonists, antidepressants, steroids
  - psychiatric: mood and anxiety disorders
  - lifestyle factors: shift work, jet-lag

Investigations

- complete sleep diary every morning for 1-2 wk
  - record bedtime, sleep latency, total sleep time, awakenings, quality of sleep
- rule out specific medical problems (e.g. CBC and differential, TSH)
- refer for sleep study, nocturnal polysomnogram, or daytime multiple sleep latency test if suspicion of sleep apnea or periodic leg movements of sleep

Treatment of Specific Problems

- primary insomnia
  - majority of cases
  - person reacts to insomnia with fear or anxiety around bedtime or with a change in sleep hygiene, which can progress to a chronic disorder (psychophysiological insomnia)
  - treat any suspected medical or psychiatric cause
  - behaviour-based treatment
    - sleep hygiene: avoid alcohol, caffeine, nicotine; comfortable sleep environment; regular sleep schedule; no napping
    - exercise regularly, avoid heavy exercise within 3 h of bedtime
    - relaxation therapy: deep breathing, meditation, biofeedback
    - stimulus control therapy: re-association of bed/bedroom with sleep, re-establishment of a consistent sleep-wake schedule, reduce activities that cue staying awake
    - sleep restriction therapy: total time in bed should closely match the total sleep time of the patient (improves sleep efficacy)
    - CBT: address inappropriate beliefs and attitudes that perpetuate dysfunctional sleep
  - pharmacologic treatment
    - short-acting benzodiazepines (e.g. lorazepam, oxazepam, temazepam) at the lowest effective dose should be used <7 consecutive nights to break cycle of chronic insomnia or to manage an exacerbation of previously controlled primary insomnia
    - non-benzodiazepines: zopiclone (Imovane®), zolpidem (Sublinox®), melatonin, low dose anti-depressants with sedating properties (amitriptyline, trazadone, mirtazapine)
    - follow-up every 2-4 wk initially (to reinforce behavioural interventions and renew/consider pharmacotherapy) then every 3 mo; if no progress or limited improvement, consider referral to sleep medicine program

- snoring
  - results from soft tissue vibration at the back of the nose and throat due to turbulent airflow through narrowed air passages
  - physical exam: obesity, nasal polyps, septal deviation, hypertrophy of the nasal turbinates, enlarged uvula and tonsils
  - investigations (only if severely symptomatic): nocturnal polysomnography and airway assessment (CT/MRI)
  - treatment
    - sleep on side (position therapy), weight loss
    - nasal dilators (noninvasive external dilator made with elastic adhesive backing applied over nasal bridge), tongue-retaining devices, mandibular advancement devices
  - at risk of developing obstructive sleep apnea

- obstructive sleep apnea (OSA)
  - apnea (no breathing for ≥10 s) resulting from upper airway obstruction due to collapse of the base of the tongue, soft palate with uvula, and epiglottis; respiratory effort is present
  - leads to a distinctive snorting, choking, awakening type pattern as the body rouses itself to open the airway (resuscitative breath)
  - apneic episodes can last from 20 s-3 min and occur 100-600 episodes/night
  - diagnosis is based on nocturnal polysomnography: >15 apneic/hypopneic episodes per hour of sleep with arousal recorded
  - consequences
    - daytime somnolence, non-restorative sleep
    - poor social and work performance
    - mood changes: anxiety, irritability, depression
    - sexual dysfunction: poor libido, impotence

Risk Factors for Obstructive Sleep Apnea

- 2% of women, 4% of men between ages 30-60
- Obesity (due to upper airway narrowing): BMI >28 kg/m² present in 60-90% of cases
- Children (commonly due to large tonsils and adenoids)
- Aging (due to decreased muscle tone)
- Persistent URTIs, allergies, nasal tumours, hypothyroidism (due to macroglossia), neuromuscular disease
- Family history
morning headache (due to hypercapnia)
HTN (2x increased risk), CAD (3x increased risk), stroke (4x increased risk), arrhythmias
OSA is an independent risk factor for CAD
pulmonary HTN, right ventricular dysfunction, cor pulmonale (due to chronic hypoxemia)
memory loss, decreased concentration, confusion
investigations
evaluate BP, inspect nose and oropharynx (enlarged adenoids or tonsils)
blood gas not helpful, TSH if clinically indicated
nocturnal polysomnography
treatment
modifiable factors: avoid sleeping supine; weight loss; avoid alcohol, sedatives, opioids; inhaled steroids if nasal swelling present; dental appliances to modify mandibular position
primary treatment of OSA is CPAP: maintains patent airway in 95% of OSA cases
surgery: somnoplasty, uvulopalatopharyngoplasty (UPPP), tonsillectomy, and adenoidectomy (in children)
report patient to Ministry of Transportation if OSA is not controlled by CPAP

Sore Throat (Pharyngitis)

Definition
- inflammation of the oropharynx
- may be caused by a wide range of infectious organisms, most of which produce a self-limited infection with no significant sequelae

Etiology
- viral: adenovirus, rhinovirus, influenza virus, RSV, EBV, coxsackie virus, herpes simplex virus, CMV, HIV
- bacterial: group A β-hemolytic Streptococcus (GABHS), group C and group β-hemolytic Streptococcus, Neisseria gonorrhoeae, Chlamydia pneumoniae, Mycoplasma pneumoniae, Corynebacterium diphtheriae

Epidemiology
- viral
  - most common cause (90% in adults is viral), occurs year round
- bacterial
  - GABHS (Group A β-Hemolytic Streptococcal Infections)
    - most common bacterial cause
    - occurs most often in winter months
    - 5-15% of adult cases and up to 50% of all pediatric cases of acute pharyngitis
    - most prevalent between 5-17 yr old

Clinical Features
- viral
  - pharyngitis, conjunctivitis, rhinorrhea, hoarseness, cough
  - nonspecific flu-like symptoms such as fever, malaise, and myalgia
  - often mimics bacterial infection
  - common viral infections
    - EBV (infectious mononucleosis)
      - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
    - coxsackie virus (hand, foot, and mouth disease)
      - primarily late summer, early fall
      - sudden onset of fever, pharyngitis, headache, abdominal pain, and vomiting
      - appearance of small vesicles that rupture and ulcerate on soft palate, tonsils, pharynx
      - ulcers are pale grey and several mm in diameter, have surrounding erythema, and may appear on hands and feet
  - coxsackie virus
    - like coxsackie virus but ulcers are fewer and larger
    - pharyngitis, tonsillar exudate, fever, lymphadenopathy, fatigue, rash
- bacterial
  - symptoms: pharyngitis, fever, malaise, headache, abdominal pain, absence of cough
  - signs: fever, tonsillar or pharyngeal erythema/exudate, swollen/tender anterior cervical nodes, halitosis
  - complications: rheumatic fever, glomerulonephritis, suppurative complications (abscess, sinusitis, otitis media, cervical adenitis, pneumonia), meningitis, impetigo

Red Flags in Patients with “Sore Throat”
- Persistence of symptoms longer than 1 wk without improvement
- Respiratory difficulty (particularly stridor, croup, etc.)
- Difficulty in handling secretions (peritonsillar abscess)
- Difficulty in swallowing (Ludwig’s angina)
- Severe pain in the absence of erythema (supraglottitis/epiglottitis)
- Palpable mass (neoplasm)
- Blood in the pharynx or ear (trauma)
Investigations
- suspected GABHS
  - see Table 29 for approach to diagnosis and management of GABHS
  - gold standard for diagnosis is throat culture
  - rapid test for streptococcal antigen: high specificity (95%) but low sensitivity (50-90%)
  - suspected EBV (infectious mononucleosis)
    - peripheral blood smear, heterophile antibody test (i.e. the latex agglutination assay or "monospot")

Table 29. Modified Centor Score: Approach to Diagnosis and Management of GABHS

<table>
<thead>
<tr>
<th>POINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cough absent?</td>
</tr>
<tr>
<td>History of fever &gt;38°C?</td>
</tr>
<tr>
<td>Tonsillar exudate?</td>
</tr>
<tr>
<td>Swollen, tender anterior nodes?</td>
</tr>
<tr>
<td>Age 3-14</td>
</tr>
<tr>
<td>Age 15-44</td>
</tr>
<tr>
<td>Age &gt;45</td>
</tr>
</tbody>
</table>

In communities with moderate levels of strep infection (10-20% of sore throats):

<table>
<thead>
<tr>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 or more</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chance patient has strep</td>
<td>1-2.5%</td>
<td>5-10%</td>
<td>11-17%</td>
<td>28-35%</td>
<td>51-53%</td>
</tr>
<tr>
<td>Suggested action</td>
<td>NO culture or antibiotic</td>
<td>Culture all, treat with antibiotics only if culture is positive</td>
<td>Culture all, treat with antibiotics on clinical grounds¹, discontinue antibiotics if culture comes back negative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹Clinical grounds include a high fever or other indicators that the patient is clinically unwell and is presenting early in the course of the illness
²If an outbreak or epidemic of illness caused by GABHS is occurring in any community, the score is invalid and should not be used

Management
- viral pharyngitis
  - antibiotics not indicated
  - symptomatic therapy: acetaminophen/NSAIDs for fever and muscle aches, decongestants
- GABHS
  - antibiotic treatment decreases severity and duration of symptoms, risk of transmission (after 24 h of treatment), and risk of rheumatic fever and suppurative complications
  - incidence of glomerulonephritis is not decreased with antibiotic treatment
  - no increased incidence of rheumatic fever with 48 h delay in antibiotic treatment; if possible, delay antibiotic treatment until culture confirms diagnosis
  - routine F/U and/or post-treatment throat cultures are not required for most patients
  - F/U throat culture only recommended for: patients with history of rheumatic fever, patients of family member(s) with history of acute rheumatic fever, suspected streptococcal carrier
- infectious mononucleosis (EBV)
  - self-limiting course; antibiotics are not indicated
  - symptomatic treatment: acetaminophen/NSAIDs for fever, pharyngitis, malaise
  - avoid heavy physical activity and contact sports for at least one month or until splenomegaly resolves because of risk of splenic rupture
  - if acute airway obstruction, give corticosteroids and consult ENT
Complementary and Alternative Medicine

Epidemiology
- 50-75% of Canadians report some use of CAM over their lifetime, and only half will disclose this use to their physician
- use is highest in Western provinces and lowest in Atlantic provinces
- more likely to be used by younger patients and those with higher education and income
- examples: chiropractic, acupuncture, massage, naturopathy, homeopathy, traditional Chinese medicine, craniosacral therapy, osteopathy

Herbal Products
- over 50% of Canadians use natural health products (NHPs)
- most commonly used include echinacea, ginseng, ginkgo, garlic, St. John's wort, and soy
- relatively few herbal products have been shown to be effective in clinical trials
- many patients believe herbal products are inherently safe and are unaware of potential side effects and interactions with conventional medicines
- all NHPs must be regulated under The Natural Health Products Regulations as of January 1, 2004, including herbal remedies, homeopathic medicines, vitamins, minerals, traditional medicines, probiotics, amino acids, and essential fatty acids (e.g. omega-3)
- always ask patients whether they are taking any herbal product, herbal supplement, or other natural remedy. Further questions may include:
  ▪ Are you taking any prescription or non-prescription medications for the same purpose as the herbal product?
  ▪ Are you allergic to any plant products?
  ▪ Are you pregnant or breastfeeding?
- information resources: National Center for CAM (www.nccam.nih.gov), Health Canada website

Table 30. Common Herbal Products

<table>
<thead>
<tr>
<th>Common Name</th>
<th>Reported Uses</th>
<th>Possible Adverse Effects</th>
<th>Possible Drug Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black Cohosh</td>
<td>Menopausal symptoms, PMS, labour induction, arthritis</td>
<td>Hepatitis, liver failure, headaches, GI discomfort, heaviness in legs, weight problems</td>
<td>None reported</td>
</tr>
<tr>
<td>Chamomile</td>
<td>Mild sedative, anxiolytic, GI complaints, common cold</td>
<td>Allergic/contact dermatitis, anaphylaxis</td>
<td>Anxiolytics, sedatives</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Common cold, flu, wound treatment, UTI, cancer</td>
<td>Hypersensitivity, hepatotoxicity with prolonged use, avoid use if immunosuppressed</td>
<td>Potentiates warfarin</td>
</tr>
<tr>
<td>Evening Primrose</td>
<td>Dysmenorrhea, menopausal sx, inflammation, allergies, eczema, arthritis, MS</td>
<td>Headache, restlessness, nausea, diarrhea, may decrease seizure threshold</td>
<td>Anticoagulants, antiplatelets</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Migraine prevention, RA, anti-inflammatory</td>
<td>Anxiety, upset stomach, skin rash, miscarriage</td>
<td>Anticoagulants, antiplatelets</td>
</tr>
<tr>
<td>Flaxseed Oil</td>
<td>Laxative, menopausal symptoms, source of omega-3 fatty acids</td>
<td>Diarrhea</td>
<td>Do not take with other medications as fibre content can bind drugs</td>
</tr>
<tr>
<td>Garlic</td>
<td>Elevated lipids, HTN, hyperglycemia, antimicrobial</td>
<td>GI irritation, contact dermatitis, may increase post-operative bleeding</td>
<td>Anticoagulants, potentiates antihypertensives</td>
</tr>
<tr>
<td>Ginger</td>
<td>Nausea, motion sickness, dyspepsia, anti-inflammatory</td>
<td>Heartburn, not to be used for morning sickness</td>
<td>None known</td>
</tr>
<tr>
<td>Ginkgo Biloba</td>
<td>Increases peripheral circulation (AD, dementia, intermittent claudication), premenstrual syndrome, vertigo</td>
<td>Headache, cramping, bleeding, mild digestive problems; reports of intracranial hemorrhage</td>
<td>Anticoagulants, thiazide diuretics, MAO inhibitors</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Energy enhancer, decreases stress, adjunct support for chemotherapy/ radiation</td>
<td>HTN, nervousness, insomnia, breakthrough bleeding, palpitations</td>
<td>Stimulant medications, antihypertensives, hormonal therapies</td>
</tr>
<tr>
<td>Glucosamine (Chondroitin)</td>
<td>Osteoarthritis</td>
<td>GI distress, headache, drowsiness, palpitations</td>
<td>Caution if shellfish allergy</td>
</tr>
<tr>
<td>Saw Palmetto</td>
<td>BPH, adjunct to finasteride</td>
<td>Mild GI distress</td>
<td>α1-adrenergics, finasteride</td>
</tr>
<tr>
<td>St. John’s Wort</td>
<td>Mild to moderate depression</td>
<td>Photosensitivity, increased liver enzymes, drowsiness, dizziness, nausea, headache</td>
<td>CNS depressants, contraindicated with indinavir</td>
</tr>
<tr>
<td>Valerian Root</td>
<td>Sedative, anxiolytic, muscle relaxant, PMS</td>
<td>Drowsiness, headache, digestive problems, paradoxical insomnia</td>
<td>CNS depressants, antihistamines</td>
</tr>
</tbody>
</table>

Table 31: Primary Care Models (Adapted from www.healthforceontario.ca)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comprehensive Care Model</strong></td>
<td></td>
</tr>
<tr>
<td>• FPs/GPs in solo practice with limited after-hours availability</td>
<td></td>
</tr>
<tr>
<td>• Payment model: fee-for-service</td>
<td></td>
</tr>
<tr>
<td><strong>Family Health Team</strong></td>
<td></td>
</tr>
<tr>
<td>• Groups of health care professionals (e.g. FPs, GPs, RNs, NPs, dieticians, social workers)</td>
<td></td>
</tr>
<tr>
<td>• Wider range of services (e.g. rehabilitation, palliative care), with increased after-hours availability</td>
<td></td>
</tr>
<tr>
<td>• Receives provincial funding for allied health</td>
<td></td>
</tr>
<tr>
<td>• Patient enrolment is strongly encouraged</td>
<td></td>
</tr>
<tr>
<td>• Payment model: paid annually per patient rostered depending on demographic category (blended capitation model)</td>
<td></td>
</tr>
<tr>
<td><strong>Family Health Group</strong></td>
<td></td>
</tr>
<tr>
<td>• Group of ≥3 FPs, can utilize nurse-staffed, telephone health advisory services to provide around the clock primary care coverage</td>
<td></td>
</tr>
<tr>
<td>• Physicians commit to enrol patients</td>
<td></td>
</tr>
<tr>
<td>• Payment model: blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives</td>
<td></td>
</tr>
<tr>
<td><strong>Family Health Network</strong></td>
<td></td>
</tr>
<tr>
<td>• Group of ≥3 FPs, can utilize nurse practitioners, with telephone health advisory services to provide around the clock primary care coverage</td>
<td></td>
</tr>
<tr>
<td>• Payment model: salary-based</td>
<td></td>
</tr>
<tr>
<td><strong>Family Health Organization</strong></td>
<td></td>
</tr>
<tr>
<td>• Same as FHT but usually larger in scale in terms of personnel</td>
<td></td>
</tr>
<tr>
<td>• Physicians commit to enrol patients</td>
<td></td>
</tr>
<tr>
<td>• Must sign governance and Family Health Organization agreements to join</td>
<td></td>
</tr>
<tr>
<td>• Payment model: blended capitation model i.e. age- and sex-adjusted base rate remuneration plus bonuses and incentives</td>
<td></td>
</tr>
</tbody>
</table>

Antimicrobial Quick Reference

<table>
<thead>
<tr>
<th>Condition</th>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RESPIRATORY/ENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Rhinitis</td>
<td>Rhinovirus, coronavirus, influenza, RSV, parainfluenza, adenovirus</td>
<td>None</td>
</tr>
<tr>
<td>Pharyngitis (sore throat)</td>
<td>Rhinovirus, adenovirus, influenza, parainfluenza, coxsackievirus, coronavirus</td>
<td>None</td>
</tr>
<tr>
<td><strong>Strep Pharyngitis</strong></td>
<td>Group A (β-Hemolytic Streptococcus)</td>
<td>Adults:</td>
</tr>
<tr>
<td></td>
<td>Children</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st line: penicillin V 40 mg/kg/d PO div bid-tid (max 750 mg/d) x 10 d (use adult dose if &gt;27 kg)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd line: erythromycin estolate 40 mg/kg/d PO div bid-tid x 10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd line: cephalexin 25-50 mg/kg/d PO div qid x 10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th line: amoxicillin 40 mg/kg/d PO div bid-tid x 10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5th line: cefprozil 15 mg/kg/d PO div bid x 10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th line: cefuroxime-AX 30-40 mg/kg/d PO div bid x 10-14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7th line: clarithromycin 15 mg/kg/d PO div bid x 10-14 d</td>
<td></td>
</tr>
<tr>
<td>Sinusitis</td>
<td>S. pneumoniae</td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>M. catarrhalis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>S. aureus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st line: amoxicillin 80 mg/kg/d PO div bid-tid x 5-10 d (max 3 g/d) x 10-14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d PO div bid (max 3 g/d) x 10-14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid x 10-14 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4th line: cefuroxime 250 mg PO qid x 10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5th line: levofloxacin 500 mg PO OD x 5-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6th line: mexitiloxacin 400 mg PO OD x 5-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Adults:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1st line: amoxicillin 500 mg PO tid x 5-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2nd line: amoxicillin/clavulanate 500 or 875 mg PO bid x 5-10 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3rd line: cefuroxime-AX 250-500 mg PO bid x 5-10 d</td>
<td></td>
</tr>
<tr>
<td>Condition</td>
<td>Microorganisms</td>
<td>Antimicrobial</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-------------------------------------</td>
<td>-------------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>RESPIRATORY/ENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute Otitis Media</td>
<td><em>S. pneumoniae</em></td>
<td>Children:</td>
</tr>
<tr>
<td></td>
<td><em>H. influenzae</em></td>
<td>Treat if under age 6 mo</td>
</tr>
<tr>
<td></td>
<td><em>M. catarrhalis</em></td>
<td>If age 6-24 mo, watchful waiting appropriate if parents can observe child for 48-72 h with appropriate medical follow-up</td>
</tr>
<tr>
<td></td>
<td>Group A Strep</td>
<td>If age &gt;24 mo, treat if worsens after 48-72 h</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
<td>10 d course if age &lt;24 mo, 5 d course if age &gt;24 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 80 mg/kg/d PO div bid (max 3 g/d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 40-80 mg/kg/d PO div bid (max 3 g/d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cefprozil 30 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3rd line: cefuroxime-AX 30-40 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 15 mg/kg/d PO div bid</td>
</tr>
<tr>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Adults:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1st line: amoxicillin 500 mg PO tid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2nd line: amoxicillin/clavulanate 500 mg PO tid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cefprozil 250-500 mg PO bid x 7-10 d</td>
</tr>
<tr>
<td></td>
<td>Chronic TM perforation or ventilation tubes: Ciprodex® otic suspension 4 drops bid x 5 d</td>
<td></td>
</tr>
<tr>
<td>Otitis Externa</td>
<td><em>P. aeruginosa</em></td>
<td>Cortisporin® otic solution 4 drops tid or qid (3 drops tid or qid for children)</td>
</tr>
<tr>
<td></td>
<td>Coliforms</td>
<td>TM defect: Ciprodex® otic suspension 4 drops bid x 5 d</td>
</tr>
<tr>
<td></td>
<td><em>S. aureus</em></td>
<td>Necrotizing (i.e. bone involvement): ciprofloxacin 750 mg PO bid x 4-8 wk</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>*H. influenzae, parainfluenza,</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>coronavirus, rhinovirus, RSV</td>
<td></td>
</tr>
<tr>
<td>Community Acquired</td>
<td><em>S. pneumoniae</em></td>
<td>1st line: amoxicillin 1,000 mg PO tid x 7-14 d</td>
</tr>
<tr>
<td>Pneumonia: Outpatient</td>
<td><em>M. pneumoniae</em></td>
<td>(for patients over age 50 where mycoplasma infection is less likely)</td>
</tr>
<tr>
<td>without Comorbidity</td>
<td><em>C. pneumoniae</em></td>
<td>erythromycin 500 mg PO qid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>clarithromycin 500 mg PO bid or 1,000 mg (ER) PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 500 mg PO on 1st d then 250 mg PO OD x 4 d or 500 mg PO OD x 3 d</td>
</tr>
<tr>
<td>Community Acquired</td>
<td><em>S. pneumoniae</em></td>
<td>2nd line: doxycycline 100 mg PO on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td>Pneumonia: Outpatient</td>
<td><em>M. pneumoniae</em></td>
<td>ANY ONE of the β-lactam agents below:</td>
</tr>
<tr>
<td>with Comorbidity</td>
<td><em>C. pneumoniae</em></td>
<td>amoxicillin 1,000 mg PO tid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td><em>H. influenzae</em></td>
<td>amoxicillin/clavulanate 500 mg PO tid or 875 mg PO bid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cefuroxime-AX 500 mg PO bid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cefprozil 500 mg PO bid x 7-14 d</td>
</tr>
<tr>
<td></td>
<td>PLUS ONE of the following:</td>
<td>clarithromycin 500 mg PO bid or 1,000 mg (ER) PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 500 mg PO OD on 1st d then 250 mg PO OD x 4 d</td>
</tr>
<tr>
<td></td>
<td>OR ANY ONE of the following:</td>
<td>doxycycline 100 mg PO bid on 1st d then 100 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td></td>
<td>OR ANY ONE of the following:</td>
<td>levofloxacin 750 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td>Dental Infections/</td>
<td>Oral Flora</td>
<td>maxifloxacin 400 mg PO OD x 7-14 d</td>
</tr>
<tr>
<td>Periapical and Periodontal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abscesses</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GASTROENTEROLOGY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea – Enteritis</td>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>Mild to moderate (i.e. &lt;3 BM/d, no blood, no fever): OTC loperamide 4 mg PO STAT then 2 mg PO after each loose stool (max 8 doses/d)</td>
</tr>
<tr>
<td></td>
<td>Campylobacter</td>
<td>OTC bismuth subsalicylate (Pepto Bismol®) 2 tabs or 30 mL repeat q30min prn (max 8 doses/d) (prevention: 2 tabs or 30 mL qid with meals and in the evening)</td>
</tr>
<tr>
<td></td>
<td>Salmonella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shigella</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Viruses</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Protozoa</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate to severe (i.e. &gt;3 BM/d, blood, fever): colfoxacin 400 mg PO single dose or 300 mg PO bid x 3 d (prevention: 300 mg PO OD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>norfoxacin 800 mg PO single dose or 400 mg PO bid x 1-3 d (prevention: 400 mg PO OD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ciprofloxacin 750 mg PO single dose or 500 mg PO bid x 1-3 d (prevention: 500 mg PO OD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>levofoxacin 500 mg PO OD x 1-3 d (prevention: 500 mg PO OD)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>azithromycin 1,000 mg PO single dose or 500 mg PO OD x 1-3 d (children: 10 mg/kg/d x 3 d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Azithromycin:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommended primarily for Thailand, India, Nepal, and Indonesia where Campylobacter resistance to quinolones is high</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Considered drug of choice for children because of safety, tolerability, and ease of administration</td>
</tr>
</tbody>
</table>
### Gastroenterology

**Diarrhea – Post Abx**  
(common with clindamycin)

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| *C. difficile* | Mild to moderate (WBC <5 x 10^9/L and Cr < 1.5 x baseline): metronidazole 500 mg PO tid or 250 mg PO qid x 10 d (children: 15-30 mg/kg/d PO div tid-qid max 4 g/d)  
Severe (WBC ≥15 x 10^9/L and Cr ≥1.5 x baseline): vancomycin 125 mg PO qid x 10-14 d (children: 40 mg/kg/d PO div tid-qid x 10-14 d max 2 g/d) |

**Peptic Ulcer Disease**  
(non-NSAID related)

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| *H. pylori* | 1st line: (PPI PO bid + amoxicillin 1,000 mg PO bid + clarithromycin 500 mg PO bid x 7 d  
(e.g. HP-PAC: lansoprazole 30 mg PO bid + amoxicillin 1,000 mg PO bid + clarithromycin 500 mg PO bid x 7 d))  
2nd line: (PPI PO bid + metronidazole 500 mg PO bid + clarithromycin 500 mg or 250 mg PO bid x 7 d)  
2nd line: (PPI PO bid + metronidazole 500 mg PO bid + amoxicillin 1,000 mg PO bid x 7 d)  
(PPI PO bid + bismuth subsalicylate 2 tabs or 30 mL qid + metronidazole 250 mg PO qid + tetracycline 500 mg PO qid x 7-14 d) |

### Genitourinary

**Head and Pubic Lice** (crabs)

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pediculus humanus capitis</td>
<td>Permethrin cream 1%: apply as liquid onto washed hair for 10 min, then rinse; repeat in 1 wk</td>
</tr>
</tbody>
</table>
| Phthirius pubis | Treat only if patient is symptomatic  
flucnornazole 150 mg PO single dose  
miconazole 2% cream (Monistat 7®): one applicator (5 g) intravaginally qhs x 7 d  
multiple other OTC azole treatments |

**Vulvovaginal Candidiasis**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>

**Bacterial Vaginosis**

<table>
<thead>
<tr>
<th>Overgrowth of:</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| *G. vaginalis* | If patient is asymptomatic, treatment is unnecessary unless high-risk pregnancy, prior IUD insertion, gynecologic surgery, induced abortion, or upper tract instrumentation  
1st line: metronidazole 500 mg PO bid x 7 d  
metronidazole 0.75% gel: one applicator (5 g) intravaginally qhs x 5 d  
clinidamycin 2% cream: one applicator (5 g) intravaginally qhs x 7 d  
2nd line: metronidazole 2 g PO single dose  
clinidamycin 300 mg PO bid x 7 d |

**Herpes**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| Herpes simplex virus | 1° episode: acyclovir 400 mg PO tid x 5-7 d  
famciclovir 250 mg PO tid x 5-7 d  
valacyclovir 500-1,000 mg PO bid x 5-7 d  
Recurrence Episode: acyclovir 400 mg PO tid x 5 d or 800 mg PO bid x 5 d or 800 mg PO tid x 2 d  
famciclovir 125 mg PO bid x 5 d  
valacyclovir 500 mg PO bid x 3 d or 1,000 mg PO OD x 3 d  
Pregnancy:  
1° episode: acyclovir 200 mg PO 5x/d x 5-10 d  
Prior infection within previous yr: acyclovir 200 mg PO qid at 36 wk  
valacyclovir 500 mg PO bid at 36 wk |

**Gonorrhea/Chlamydia**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| *N. gonorrhoeae* | Ceftriaxone 250 mg IM x 1 dose + azithromycin 1 g PO  
single dose or doxycycline 100 mg PO bid x 7 d |

### Dermatologic

**Mastitis**

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| *S. aureus* | cloxacillin 500 mg PO qid x 7 d  
cephalexin 500 mg PO qid x 7 d |
| *S. pyogenes* | clotrimazole 1% cream bid  
ketocnazole 2% cream bid |
| Trichophyton | cloxacillin 500 mg PO qid x 7 d  
cephalexin 500 mg PO qid x 7 d |

**Tinea Cruris/Pedis** (jock itch/athlete’s foot)

<table>
<thead>
<tr>
<th>Microorganisms</th>
<th>Antimicrobial</th>
</tr>
</thead>
</table>
| *S. aureus* | Children  
1st line: cephalexin 50-100 mg/kg/d div qid x 10-14 d  
2nd line: cloxacillin 50 mg/kg/d div qid x 10-14 d  
clinidamycin 25 mg/kg/d x 10-14 d |
| Group A Streptococcus | Adults  
1st line: cephalexin 500 mg PO qid x 10-14 d  
2nd line: cloxacillin 500 mg PO qid x 10-14 d  
clinidamycin 300 mg PO x 10-14 d |

---

*All doses are adult doses unless otherwise specified*  
*This chart is not all-encompassing and is non-inclusive of special exceptions (i.e. pregnancy, poor renal clearance, etc.)*  
*Comorbidities include: COPD (received steroids within the last 3 mo), liver or renal disease, CHF, DKA, malignancy, alcoholism, asplenia, immunosuppressing conditions, malnutrition, hospitalization in past 3 mo or nursing home*


Montgomery L, Scoville C. What is the best way to evaluate acute diarrhea? J Fam Pract 2002;51.


Ebell MH. Treating adult women with suspected UTI. Am Fam Phys 2006;73:293-296.


Demire F. The 5-minute clinical consultation, 18th ed. Lippincott Williams & Wilkins, 2009.


Anatomy Review

Overview of Gastrointestinal Tract

- the gastrointestinal tract runs from mouth to anus ("gum to bum")

<table>
<thead>
<tr>
<th>Organ</th>
<th>Function</th>
<th>Blood Supply</th>
<th>Innervation</th>
<th>Histology and Structural Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophagus</td>
<td>• Muscular tube approximately 25 cm long with a diameter of 2 cm</td>
<td>• Arterial: left gastric artery and left inferior phrenic artery</td>
<td>• Parasympathetic innervation via anterior and posterior gastric nerves (vagal trunks)</td>
<td>• Mucosa: stratified squamous epithelium</td>
</tr>
<tr>
<td></td>
<td>• Extends from pharynx to the stomach</td>
<td>• Venous: Left gastric vein → portal venous system</td>
<td>• Sympathetic innervation via thoracic trunks of the greater splanchnic nerves</td>
<td>• Submucosa: connective tissue, lymphocytes, plasma cells, nerve cells</td>
</tr>
<tr>
<td>Stomach</td>
<td>• Delivers food to intestine for digestion and absorption</td>
<td>• Esophageal veins → ayguses vein → IVC (systemic)</td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>• Muscularis propria (muscularis externa); inner circular, outer longitudinal muscle</td>
</tr>
<tr>
<td></td>
<td>• Secretes acid, probably to reduce enteric infections/pneumonia; facilitate digestion of protein/iron/B₁₂</td>
<td></td>
<td>• Sympathetic innervation via celiac plexus (from T6-T9)</td>
<td>• Upper 1/3: striated muscle</td>
</tr>
<tr>
<td></td>
<td>• Secretes intrinsic factor to facilitate B₁₂ absorption</td>
<td></td>
<td>• Greater curvature</td>
<td>• Middle 1/2: transition zone</td>
</tr>
<tr>
<td></td>
<td>• Minor contribution to initial protein digestion via pepsin</td>
<td></td>
<td>• Right and left gastro-omental (gastroepiploic) arteries (from gastroduodenal and splenic arteries respectively)</td>
<td>• Lower 1/3: smooth muscle</td>
</tr>
<tr>
<td>Duodenum</td>
<td>• Modulates enteral pH via secretin → decreased gastric acid secretion, increased bicarbonate secretion</td>
<td>• Lesser curvature</td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>5 parts</td>
</tr>
<tr>
<td></td>
<td>• Secretes CCK to stimulate bile secretion</td>
<td>• Right and left gastric arteries (from celiac trunk)</td>
<td>• Sympathetic innervation via celiac plexus</td>
<td>• Cardia</td>
</tr>
<tr>
<td></td>
<td>• Site of iron absorption</td>
<td>• Greater curvature</td>
<td>• Fundus: short and posterior gastric arteries (from the splenic artery)</td>
<td>• Fundus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>• Body</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Branches of celiac artery and superior mesenteric artery</td>
<td>• Antrum</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>• Pylorus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>4 parts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Branches of celiac artery and superior mesenteric artery</td>
<td>• Superior (5 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>• Descending (7-10 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>• Horizontal (6-8 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Branches of celiac artery and superior mesenteric artery</td>
<td>• Ascending (9 cm)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Parasympathetic innervation via vagus nerve</td>
<td>1st part is infraportal, rest is retroperitoneous</td>
</tr>
<tr>
<td>Organ</td>
<td>Function</td>
<td>Blood Supply</td>
<td>Innervation</td>
<td>Histology and Structural Features</td>
</tr>
<tr>
<td>---------------</td>
<td>---------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>--------------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Absorption of sodium, water, and nutrients (protein, carbohydrates, fat, folic acid, and vitamin A, B, C, D, E, K)</td>
<td>Superior mesenteric artery</td>
<td>Parasympathetic innervation via fibers of the posterior vagal trunk</td>
<td>Deep red colour, 2-4 cm in thickness, thick and heavy wall, Plicae circulares are large, tall, and closely packed, Has long vasa recta, Scant fat in mesentery, Scant Peyers patches</td>
</tr>
<tr>
<td>Ileum</td>
<td>Absorption of sodium, water, nutrients, soluble vitamins (only site of vitamin B₁₂ absorption), and bile salts (entero-hepatic circulation)</td>
<td>Superior mesenteric artery</td>
<td>Same as jejunum</td>
<td>When compared to jejunum: Paler pink colour, 2-3 cm in thickness, Thin and light walls, Plicae circulares are small and sparse, Contains more mesenteric fat, Many Peyers patches</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>Absorption of water (5-10% of total water), Bacteria: further digestion of chyme and metabolism of undigested CHO to short chain fatty acids, Formation and storage of feces</td>
<td>Branches of superior and inferior mesenteric arteries, Rectal blood supply: sigmoid, right pudendal, and rectal arteries</td>
<td>Parasympathetic innervation via vagus nerve, Sympathetic innervation via greater and lesser splanchnic nerves</td>
<td>Consists of cecum, colon (ascending, transverse, descending, and sigmoid), rectum and anal canal, Features include teniae coli, hastra, and omental appendices</td>
</tr>
<tr>
<td>Liver</td>
<td>Glucose homeostasis, Plasma protein synthesis, Lipid and lipoprotein synthesis, Bile acid synthesis and secretion, Vitamin A, D, E, K, B₁₂ storage, Biotransformation, detoxification, Excretion of compounds</td>
<td>2 sources, Portal vein (75-80%), Hepatic artery (20-25%)</td>
<td>Sympathetic innervation via fibers of the celiac plexus, Parasympathetic innervation via fibers of the anterior and posterior vagal trunks</td>
<td>Largest internal organ, Consisted of 4 lobes (left, right, caudate, quadrate), and divided into 8 segments</td>
</tr>
<tr>
<td>Biliary Tract</td>
<td>Gallbladder functions to store and release bile that is produced in the liver, Bile is used to emulsify fat and is composed of cholesterol, lecithin, bile acids, and bilirubin, CCK stimulates gallbladder emptying while trypsin and chymotrypsin inhibit bile release</td>
<td>Cystic artery</td>
<td>Parasympathetic innervation via vagus nerve, Sympathetic and visceral innervation via celiac nerve plexus, Somatic afferent fibers via right phrenic nerve</td>
<td>Consists of the hepatic ducts (intrahepatic, left, right, and common), gallbladder, cystic duct, common bile duct, and ampulla of Vater</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Endocrine function: islets of Langerhans produce glucagon, insulin, and somatostatin (from the α, β, and δ cells, respectively), Exocrine function: digestive enzymes are produced including amylase, lipase, trypsin, chymotrypsin, and carboxypeptidase</td>
<td>Anterior superior pancreaticoduodenal artery (from the celiac trunk), Anterior inferior pancreaticoduodenal artery (from the superior mesenteric artery), Dorsal pancreatic artery (from the splenic artery), Pancreatic veins drain into the portal, splenic, and superior mesenteric veins</td>
<td>Parasympathetic innervation via vagus nerve, Sympathetic innervation via abdominopelvic splanchnic nerves</td>
<td>4 parts of pancreas: head (includes uncinate process), neck, body, and tail, (Major) pancreatic duct connecting to common bile duct prior to ampulla of Vater, Accessory pancreatic duct connected directly to duodenum</td>
</tr>
</tbody>
</table>

### Visualizing the GI Tract

- see Medical Imaging, MI10

### Esophagus, Stomach, Duodenum

- **OGD**: best visualization of mucosa; also allows for therapeutic intervention (e.g. banding varices, thermal therapy/clipping/injecting bleeding ulcers, and dilatation e.g. treatment of esophageal strictures)
- consider barium swallow first if dysphagia, decreased level of consciousness (increases risk of aspiration), inability to cooperate (increases risk of pharyngeal trauma during intubation), possibility of fistulas
- endotracheal intubation first if massive upper GI bleed, acidemia, or inability to protect airway
Small Bowel
- most difficult to visualize, especially if mucosal detail is needed
- CT enterography more accurate than small bowel follow through, but both have low sensitivity
- MRI small bowel imaging increasingly available, especially useful if radiation exposure is an issue (e.g. young patient, multiple radiological images already done)
  - note: MRI enteroclysis: luminal contrast administered by nasojejunal tube to dilate the small bowel - disliked by both radiologist and patient, but may improve sensitivity
- "double balloon" enteroscopy (enteroscope with proximal and distal balloons to propel endoscope into jejunum from mouth or into jejunum/ileum or into ileus from anus) may be most sensitive but currently available only in selected centres; technically demanding
- wireless endoscopy capsule (26 x 11 mm capsule is swallowed, transmits images to a computer; contraindicated in bowel obstruction) is also accurate in diagnosis but unable to provide any therapeutic intervention

Colon and Terminal Ileum
- colonscopy, with biopsy if required; contraindicated in perforation, acute diverticulitis, and severe colitis (increased risk of perforation)
- CT colonography ("virtual colonoscopy") more accurate in diagnosing diverticulosis, extrinsic pressure on colon (e.g. ovarian cancer compressing sigmoid colon), and fistulae; increasing evidence for use in colorectal cancer screening, especially for assessment of right side of colon in cases where colonscopy is less sensitive

Pancreatic/Biliary Duct
- MRCP almost as sensitive as ERCP in determining if bile duct obstruction present, but less accurate in determining cause of obstruction (tumour, stone, stricture)
- ERCP if endoscopic draining necessary, strong suspicion of stone, obstruction requiring stenting, or if tissue sampling required

Differential Diagnosis of Common Presenting Complaints

See General Surgery, Acute Abdominal Pain, GS4

Table 2. Differential Diagnosis of Common Presenting Complaints

<table>
<thead>
<tr>
<th>CHRONIC/RECURRENT ABDOMINAL PAIN</th>
<th>Inflammatory</th>
<th>Neoplastic/Vascular</th>
<th>Toxin</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>PUD</td>
<td>Recurrent bowel obstruction</td>
<td>Sickle cell anemia</td>
<td>Lead poisoning</td>
<td>Mittelschmerz</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Mesenteric ischemia</td>
<td></td>
<td></td>
<td>Endometriosis</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
<td></td>
<td>Porphyria</td>
</tr>
<tr>
<td>Chronic pancreatitis</td>
<td></td>
<td></td>
<td></td>
<td>IBS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ACUTE DIARRHEA</th>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Causes of bloody diarrhea</td>
<td>Bacterial</td>
<td>Viral</td>
</tr>
<tr>
<td>Shigella*</td>
<td>E. histolytica*</td>
<td>Rotavirus</td>
</tr>
<tr>
<td>Salmonella*</td>
<td>amoebiasis</td>
<td>Norwalk</td>
</tr>
<tr>
<td>Campylobacter*</td>
<td>Strongyloides</td>
<td>CMV</td>
</tr>
<tr>
<td>Yersinia*</td>
<td></td>
<td>Drugs</td>
</tr>
<tr>
<td>E. coli (HEC)</td>
<td></td>
<td>Antibiotics</td>
</tr>
<tr>
<td>0157:H7*</td>
<td></td>
<td>Colchicine</td>
</tr>
<tr>
<td>C. difficile</td>
<td></td>
<td>Laxatives</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td>Antacids (magnesium)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CHRONIC DIARRHEA</th>
<th>Inflammatory</th>
<th>Organic</th>
<th>Steatorrheic</th>
<th>Osmotic</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Causes of bloody diarrhea</td>
<td>IBD</td>
<td>Stimulant laxatives</td>
<td>Giardia lamblia</td>
<td>Osmotic laxatives</td>
<td>IBS</td>
</tr>
<tr>
<td>Infectious</td>
<td></td>
<td>Post-ileal resection</td>
<td>Celiac sprue</td>
<td>Lactose</td>
<td>Constipation</td>
</tr>
<tr>
<td>(C. difficile, TB, CMV, HSV)</td>
<td></td>
<td>cholecystectomy (bile salts)</td>
<td>Chronic pancreatitis</td>
<td>intolerance</td>
<td>(overflow diarrhea)</td>
</tr>
<tr>
<td>Ischemic bowel colitis</td>
<td></td>
<td>Bacterial toxins</td>
<td>Chronic</td>
<td>Chevving gum</td>
<td>Anal sphincter dysfunction</td>
</tr>
<tr>
<td>Neoplasia</td>
<td></td>
<td>Vasculitis</td>
<td>cholestasis</td>
<td>(sorbitol, mannitol)</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td></td>
<td>Neoplasia (Colon Ca, Carcinoid, VPoma)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Addison’s disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Congenital syndromes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Causes of bloody diarrhea
- Rule out IBD when patient presents with bloody diarrhea
<table>
<thead>
<tr>
<th>Table 2. Differential Diagnosis of Common Presenting Complaints (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CONSTIPATION</strong>: if no associated rectal bleeding/weight loss, etc., usually no cause found</td>
</tr>
<tr>
<td>- Colorectal cancer</td>
</tr>
<tr>
<td>- Stricture</td>
</tr>
<tr>
<td>- Extrinsic compression</td>
</tr>
<tr>
<td>- Anal disease</td>
</tr>
<tr>
<td>- Rectocele</td>
</tr>
<tr>
<td>- Medications (narcotics, antidepressants, calcium channel blockers)</td>
</tr>
<tr>
<td>- Metabolic (DM, thyroid, hypercalcemia)</td>
</tr>
<tr>
<td>- Neurologic (Parkinson’s, MS, stroke)</td>
</tr>
<tr>
<td>- Collagen vascular disease (scleroderma, dermatomyositis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>NAUSEA/VOMITING</strong></th>
<th>With Abdominal Pain</th>
<th>Without Abdominal Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With Relieved by Vomiting</strong></td>
<td><strong>Not Relieved by Vomiting</strong></td>
<td><strong>Headache/Dizziness</strong></td>
</tr>
<tr>
<td>Gastric outlet obstruction</td>
<td>Gallbladder disease</td>
<td>Cerebral tumour</td>
</tr>
<tr>
<td>Small bowel obstruction</td>
<td>Pancreatitis</td>
<td>Migraine</td>
</tr>
<tr>
<td>GERD (regurgitation more common)</td>
<td>Hepatitis</td>
<td>Vestibular disease</td>
</tr>
<tr>
<td></td>
<td>Infectious</td>
<td>Increased ICP</td>
</tr>
<tr>
<td></td>
<td>Gastroenteritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DYSPEPSIA</strong></th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Functional dyspepsia</td>
<td>Angina</td>
<td>Giardia lamblia</td>
<td></td>
</tr>
<tr>
<td>Drug side effect</td>
<td>Crohn’s disease</td>
<td>Malabsorption (celiac sprue)</td>
<td></td>
</tr>
<tr>
<td>Peptic ulcer</td>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GERD</td>
<td>Gallstones</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aerophagia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>UPPER GI BLEED</strong></th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulcers (H. pylori, ASA, NSAIDs)</td>
<td>Tumours</td>
<td>Aorto-enteric fistulas</td>
<td></td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>Arteriovenous malformation</td>
<td>Hemobilia</td>
<td></td>
</tr>
<tr>
<td>Mallory-Weiss tears</td>
<td>Deulphoy’s lesion (arterial)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosive esophagitis</td>
<td>Gastric antral vascular ectasia (GAVE)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erosive gastritis</td>
<td>Portal hypertensive gastropathy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>LOWER GI BLEED</strong></th>
<th>Common</th>
<th>Uncommon</th>
<th>Rare</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diverticulosis</td>
<td>Upper GI bleed (brisk)</td>
<td>Intussusception</td>
<td></td>
</tr>
<tr>
<td>Ischemia</td>
<td>Post-polypectomy</td>
<td>Vascular sludges</td>
<td></td>
</tr>
<tr>
<td>Angiodysplasia (elderly)</td>
<td>Radiation colitis</td>
<td>Stercoral ulcer</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>IBD</td>
<td>Coagulopathies</td>
<td></td>
</tr>
<tr>
<td>Anorectal (hemorrhoids, fissure, ulcer)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>DYSPHAGIA</strong></th>
<th>Mechanical (Solids)</th>
<th>Motility (Solids and Liquids)</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peptic stricture/cancer</td>
<td>Achalasia</td>
<td>Foreign body</td>
<td></td>
</tr>
<tr>
<td>Eosinophilic esophagitis</td>
<td>Diffuse esophageal spasm</td>
<td>Eosinophilic esophagitis</td>
<td></td>
</tr>
<tr>
<td>Extrinsic compression</td>
<td>Scleroderma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schatzki ring/esophageal web</td>
<td>Zenker’s diverticulum</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>ODYNOPHAGIA</strong></th>
<th>Infection</th>
<th>Inflammation/Ulceration</th>
<th>Drugs</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida</td>
<td>Caustic damage</td>
<td>Quinidine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Herpes</td>
<td>Eosinophilic esophagitis</td>
<td>Iron</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CMV (common in those who are immunosuppressed)</td>
<td></td>
<td>Vitamin C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Commonly Forgotten Causes of Vomiting**
- Drugs
- Uremia
- CNS Disease
- Pregnancy

**Difference Between Dysphagia and Odynophagia**
- **Dysphagia**: Difficulty swallowing. May suggest difficulty in the passage of solids or liquids from the mouth to the stomach, lack of pharyngeal sensation, or other inadequacy of the swallowing mechanism
- **Odynophagia**: Pain when swallowing
### Table 2. Differential Diagnosis of Common Presenting Complaints (continued)

<table>
<thead>
<tr>
<th>Abdominal Distention</th>
<th>Fluid (Ascites)</th>
<th>Flatulence</th>
<th>Feces</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Portal HTN</td>
<td>Normal Portal Pressure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Cancer (especially ovarian)</td>
<td>Pancreatitis</td>
<td>TB</td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>Functional bowel disease (e.g. IBS)</td>
<td>Fibre</td>
<td>Lactose intolerance</td>
<td>Chewing gum (e.g. sorbitol, mannitol)</td>
</tr>
<tr>
<td>Hepatic vein thrombosis</td>
<td>Constipation</td>
<td>Colonic obstruction</td>
<td>Dysmotility</td>
<td>Pregnancy (fetus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Obesity (fat)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Large tumours (fatal growth)</td>
</tr>
</tbody>
</table>

### JAUNDICE (UNCONJUGATED BILIRUBIN)

<table>
<thead>
<tr>
<th>Overproduction</th>
<th>Decreased Hepatic Intake</th>
<th>Decreased Conjugation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemolysis</td>
<td>Gilbert’s syndrome</td>
<td>Drug inhibition (e.g. chloramphenicol)</td>
</tr>
<tr>
<td>Ineffective erythropoiesis (e.g. megaloblastic anemias)</td>
<td>Drugs (e.g. rifampin)</td>
<td>Crigler-Najjar syndromes type I and II</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gilber’s syndrome</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neonatal jaundice</td>
</tr>
</tbody>
</table>

### JAUNDICE (CONJUGATED BILIRUBIN)

<table>
<thead>
<tr>
<th>Common</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatocellular disease</td>
<td>Intraductal obstruction</td>
</tr>
<tr>
<td>Drugs</td>
<td>Gallstones</td>
</tr>
<tr>
<td>Cirrhosis (any cause)</td>
<td>Biliary stricture</td>
</tr>
<tr>
<td>Inflammation (hepatitis, any cause)</td>
<td>Parasites</td>
</tr>
<tr>
<td>Infiltrative (e.g. hemochromatosis)</td>
<td>Malignancy (cholangiocarcinoma)</td>
</tr>
<tr>
<td>Familial disorders (e.g. Rotor syndrome, Dubin-Johnson syndrome, cholestasis of pregnancy)</td>
<td>Sclerosing cholangitis</td>
</tr>
<tr>
<td>PBC</td>
<td>Extraductal obstruction</td>
</tr>
<tr>
<td>PSC</td>
<td>Malignancy (e.g. pancreatic cancer, lymphoma)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>Metastases in peri-portal nodes</td>
</tr>
<tr>
<td>Post-operative/TPN</td>
<td>Inflammation (e.g. pancreatitis)</td>
</tr>
</tbody>
</table>

---

## Esophagus

### Gastroesophageal Reflux Disease

**Definition**
- condition in which the stomach contents (most characteristically acid) moves backwards from the stomach into the esophagus (the tube from the mouth to the stomach)

**Etiology**
- inappropriate transient relaxations of LES – most common cause
- low basal LES tone (especially in scleroderma)
- contributing factors include: delayed esophageal clearance, delayed gastric emptying, obesity, pregnancy, acid hypersecretion (rare) from Zollinger-Ellison syndrome (gastrin-secreting tumour)
- hiatus hernia worsens reflux, does not cause it (see General Surgery, GS13)

**Clinical Features**
- “heartburn” (pyrosis) and acid regurgitation (together are 80% sensitive and specific for reflux)
- ± sour regurgitation, water brash, sensation of a lump in the throat (globus sensation), and frequent belching
- non-esophageal symptoms (see G7) are increasingly recognized of being poor predictors of reflux

**Foods/Substances that Aggravate GERD Symptoms**
- EtOH
- Caffeine
- Tobacco
- Fatty/fried foods
- Chocolate
- Peppermint
- Spicy foods
- Citrus fruit juices

**GERD signs/symptoms**

- **Respiratory**
  - Chronic cough
  - Wheezing
  - Aspiration pneumonia

- **Non-respiratory**
  - Sore throat
  - Hoarseness
  - Dental erosions

- **Typical**
  - Heartburn
  - Acid regurgitation

- **Atypical**
  - Chest pain
  - Dysphagia (late)
  - Odynophagia (rare)

**Dyspepsia** = postprandial fullness, early satiety, epigastric pain, or burning

---

*Figure 2. Signs and symptoms of GERD*
Investigations

- usually, a clinical diagnosis is sufficient based on symptom history and relief following a trial of pharmacotherapy (PPI: symptom relief 80% sensitive for reflux)
- gastroscopy indications (*Ann Intern Med* 2012;157:808-816)
  - absolute indications
    - heartburn accompanied by red-flags (bleeding, weight loss, etc.)
    - persistent reflux symptoms or prior severe erosive esophagitis after therapeutic trial of 4-8 wk of PPI 2x daily
    - history of esophageal stricture with persistent dysphagia
    - repeat endoscopy after 6-8 wk of PPI therapy is indicated if: 1) severe esophagitis (because it can mask Barrett’s esophagus) or 2) known Barrett’s esophagus or 3) recurrence of symptoms
- esophageal manometry (study of esophageal motility)
  - may be done to diagnose abnormal peristalsis and/or decreased LES tone, but cannot detect presence of reflux; indicated before surgical fundoplication to ensure intact esophageal function
- surgical fundoplication (wrapping of gastric fundus around the lower end of the esophagus)
  - more likely to alleviate symptoms if lower esophageal pressure is diminished; less likely to be successful if abnormal peristalsis
- 24 h pH monitoring; most accurate test for reflux, but not required or performed in most cases
- most useful if PPIs do not improve symptoms

Treatment

- PPIs are the most effective therapy and usually need to be continued as maintenance therapy
- on-demand: antacids (Mg(OH)2, Al(OH)3, alginate), H2-blockers, or PPIs can be used for NERD
- diet helps symptoms, not the disease; avoid alcohol, coffee, spices, tomatoes, and citrus juices
- only beneficial lifestyle changes are weight loss (if obese) and elevating the head of bed (if nocturnal symptoms)
- symptoms may recur if therapy is discontinued

Complications

- esophageal stricture disease – scarring can lead to dysphagia (solids)
- ulcer
- bleeding
- Barrett’s esophagus and esophageal adenocarcinoma – gastroscopy is recommended for patients with chronic GERD or symptoms suggestive of complicated disease (e.g. anorexia, weight loss, bleeding, dysphagia)

Barrett’s Esophagus

Definition

- metaplasia of normal squamous esophageal epithelium to abnormal columnar epithelium containing-type intestinal mucosa (intestinal metaplasia)

Etiology

- thought to be acquired via long-standing GERD and consequent damage to squamous epithelium

Epidemiology

- in North America and Western Europe, 0.5-2.0% of adults are thought to have Barrett’s esophagus
- up to 10% of GERD patients will have already developed BE by the time they seek medical attention
- more common in males, age >50, Caucasians, smokers, overweight, hiatus hernia, and long history of reflux symptoms

Pathophysiology

- endoscopy shows erythematous epithelium in distal esophagus; diagnosis of BE relies on biopsy demonstrating the presence of specialized intestinal epithelium of any length within the esophagus
- BE predisposes first to premalignant changes characterized as low or high-grade dysplasia, which then progresses to adenocarcinoma

Gastroesophageal Reflux Disease

- Gastroscopy
  - Non-erosive reflux disease (NERD)
    - Aim for symptom relief only; proton pump inhibitor PRN
  - Esophagitis
    - Esophageal inflammation
      - Aim to heal inflammation; proton pump inhibitor indefinitely or surgical fundoplication

Esophageal damage from reflux is most severe at first gastroscopy, therefore gastroscopy is necessary only once for patients with NERD

Up to 25% of patients with Barrett’s esophagus do not report symptoms of GERD

Impact of Endoscopic Surveillance on Mortality from Barrett’s Esophagus - Associated Esophageal Adenocarcinomas

*Gastroenterology* 2013;145:312-319

There is no question that Barrett’s esophagus (BE) increases the incidence of esophageal adenocarcinoma, which can be recognized early on with a safe procedure, endoscopy. Indeed, because early cancer is often asymptomatic and curable, most clinicians recommend period upper endoscopy. Yet Corley et al. found no difference in endoscopy rates in BE patients who died of esophageal adenocarcinomas compared to BE patients who died of other diseases. Perhaps this result is due to statistics, but as the accompanying editorial emphasizes (*Gastroenterology* 2013; 145:273-8) at the very least this finding should question the value of a screening program. In fact, there are multiple other lines of evidence indicating that endoscopic surveillance is of marginal benefit at most. Possible explanations for this disappointing finding include: most esophageal adenocarcinomas may not arise from BE, esophageal carcinoma is too rare a cause of death in BE, morbidity from esophageal cancer treatments, or that endoscopic screening is just not that effective in the real world. The situation is analogous to the disappointing value of serum PSA screening for prostate cancer. Therefore, adoption of screening programs require more than theoretical calculations.
**Significance**
- Rate of malignant transformation is approximately 0.12% per yr for all BE patients prior to dysplasia.
- Risk of malignant transformation in high-grade dysplasia is significantly higher; studies have reported a 32-59% transformation rate over 5-8 yr of surveillance.
- Increased gastric acid secretion is more frequently associated with Barrett's esophagus as opposed to reflux alone.

**Treatment**
- Acid suppressive therapy with high-dose PPI indefinitely (or surgical fundoplication).
- Endoscopy every 3 yr if no dysplasia.
- High grade dysplasia: regular and frequent surveillance with intensive biopsy, endoscopic ablation/resection, or esophagectomy produce similar outcomes; however, evidence increasingly favouring endoscopic ablation with mucosal resection or radiofrequency ablation.
- If low grade dysplasia, both surveillance and endoscopic ablation/resection are satisfactory options.

---

**Dysphagia**

**Definition**
- Difficulty swallowing, globus sensation.

---

**Esophageal Motor Disorders**

**Symptoms**
- Dysphagia with solids and liquids.
- Chest pain (in some disorders).

**Diagnosis**
- Motility study (esophageal manometry).
- Barium swallow sometimes helpful.

**Causes** (see Table 3)
- Idiopathic.
- Achalasia (painless).
- Scleroderma (painless).
- DM.
- DES: rare and can be difficult to diagnose due to intermittent presentation.
Table 3. Esophageal Motor Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Achalasia</th>
<th>Scleroderma</th>
<th>Diffuse Esophageal Spasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Failure of smooth muscle relaxation at LES</td>
<td>See Rheumatology, RH13 Systemic disease characterized by vasculopathy and tissue fibrosis (especially skin thickening)</td>
<td>Normal peristalsis interspersed with frequent, repetitive, spontaneous, high pressure, non-peristaltic waves (tertiary peristalsis)</td>
</tr>
<tr>
<td>Etiology</td>
<td>Usually idiopathic</td>
<td>Involves autoimmune, genetic, hormonal, and environmental factors</td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Inflammatory degeneration of Auerbach’s plexus → increase in LES pressure, incomplete relaxation of LES with swallowing, aperistalsis</td>
<td>Blood vessel damage → intramural neuronal dysfunction → distal esophageal muscle weakening → aperistalsis and loss of LES tone → reflux → stricture → dysphagia</td>
<td>Potential mechanisms include impaired inhibitory innervation to esophageal body, malfunction in endogenous nitric oxide synthesis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>CXR: no air in stomach, dilated esophagus</td>
<td>Clinical features of scleroderma</td>
<td>Barium x-ray: “Corkscrew pattern”</td>
</tr>
<tr>
<td></td>
<td>Barium studies: esophagus terminates in narrowing at LES (“bird’s beak”)</td>
<td>Manometry: decreased pressure in LES, decreased peristalsis in body of esophagus</td>
<td>Manometry: &gt;30% (but &lt;100%) of esophageal contractions are aperistaltic</td>
</tr>
<tr>
<td></td>
<td>Endoscopy: normal mucosa</td>
<td></td>
<td>Endoscopy: normal mucosa</td>
</tr>
<tr>
<td></td>
<td>Manometry: definitive diagnosis (signs listed above)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Dilatation of LES with balloon, ± GERD prophylaxis, 50% good response, can repeat, risk of perforation (5%)</td>
<td>Medical: aggressive GERD therapy (PPIS bid)</td>
<td>Reassurance not cardiac pain</td>
</tr>
<tr>
<td></td>
<td>Injection of botulinum toxin into LES (temporary)</td>
<td>Surgery: anti-reflux surgery (gastroplasty, last resort)</td>
<td>Medical: nitrates, calcium channel blockers, anticholinergics have variable benefit</td>
</tr>
<tr>
<td></td>
<td>Surgery (myotomy)</td>
<td></td>
<td>Surgical: long esophageal myotomy if unresponsive to above treatment (rarely helpful); balloon dilatation</td>
</tr>
</tbody>
</table>

Esophageal Diverticula

Definition
- outpouchings of one or more layers of the esophageal tract

Clinical Features
- commonly associated with motility disorders
- dysphagia, regurgitation, retrosternal pain, intermittent vomiting, may be asymptomatic

Classification
- classified according to location
  - pharyngoesophageal (Zenker’s) diverticulum
    - most frequent form of esophageal diverticulum
    - posterior pharyngeal outpouching most often on the left side, above cricopharyngeal muscle and below the inferior pharyngeal constrictor muscle
    - symptoms: dysphagia, regurgitation of undigested food, halitosis
    - treatment: endoscopic or surgical myotomy of cricopharyngeal muscle ± surgical excision of sac
  - mid-esophageal diverticulum
    - secondary to mediastinal inflammation (“traction” diverticulae), motor disorders
    - usually asymptomatic; no treatment required
  - just proximal to LES (pulsatile type)
    - usually associated with motor disorders
    - usually asymptomatic; no treatment required

Peptic Stricture (from Esophagitis)
- presents as dysphagia alongside a long history of reflux symptoms, but reflux symptoms may disappear as stricture develops
- diagnosed with endoscopy or barium study if endoscopy contraindicated or unavailable

Treatment
- endoscopic dilatation and indefinite PPI
- anti-reflux surgery (fundoplication) if above treatment unsuccessful
Esophageal Carcinoma

- see General Surgery, GS15

Webs and Rings

- web = partial occlusion (upper esophagus)
- ring = circumferential narrowing (lower esophagus)

Clinical Features
- asymptomatic with lumen diameter >12 mm, provided peristalsis is normal
- dysphagia with large food boluses
- Schatzki ring
  - mucosal ring at squamo-columnar junction above a hiatus hernia
  - causes intermittent dysphagia with solids
  - treatment involves disrupting ring with endoscopic bougie

Infectious Esophagitis

Definition
- severe mucosal inflammation and ulceration as a result of a viral or a fungal infection

Risk Factors
- DM
- chemotherapeutic agents
- immunocompromised states

Symptoms
- characteristically odynophagia, less often dysphagia
- diagnosis is via endoscopic visualization and biopsy

Appearance
- Candida (most common): whitish-yellow plaques without visible ulceration or inflammation
- Herpes (second most common), CMV: focal ulcers

Treatment
- Candida: nystatin swish and swallow, ketoconazole, fluconazole
- Herpes: often self-limiting; acyclovir, valacyclovir, famciclovir
- CMV: IV gancyclovir, foscarnet, or oral valganciclovir

Stomach and Duodenum

Dyspepsia

Definition
- group of symptoms characterized by discomfort, location in the upper epigastrium, usually following meals; most characteristic symptom is fullness, but can also be a burning, true pain
- multiple causes: esophagitis, peptic ulcer, stomach cancer, drugs, but overall functional disease is most common

History and Physical Exam
- history: most important are age, associated symptoms (such as weight loss and vomiting), and drugs (especially NSAIDs)
- physical exam: adenopathy, abdominal mass/organomegaly, Carnett’s sign (if pain is due to abdominal wall muscle problem then the pain will increase during muscle contraction, such as during a sit-up)

Investigations
- laboratory: usual (CBC, liver enzymes, glucose, Cr, etc.), amylase, albumin, calcium, protein electrophoresis, TSH, Helicobacter serology
- consider trial of empiric anti-secretory drug therapy, non-invasive testing for H. pylori infection, endoscopy, barium radiography (rarely done nowadays)
Stomach

- primary function is mechanical grinding of food facilitating early enzymatic digestion into chyme and propulsion into duodenum (motor function), but also releases secretions

<table>
<thead>
<tr>
<th>Table 4. Cells of the Gastric Mucosa</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cell Type</strong></td>
</tr>
<tr>
<td>Parietal cells</td>
</tr>
<tr>
<td>Chief cells</td>
</tr>
<tr>
<td>G-cells</td>
</tr>
<tr>
<td>Superficial epithelial cells</td>
</tr>
<tr>
<td>Neuroendocrine cells</td>
</tr>
</tbody>
</table>

![Figure 5. Stimulation of H⁺ secretion from the parietal cell](image)

Gastritis

**Definition**
- defined histologically: inflammation of the stomach mucosa

**Etiology**
- some causative agents may play a role in more than one type of gastritis and an individual patient may have histopathological evidence of more than one type of gastritis

<table>
<thead>
<tr>
<th>Table 5. Updated Sydney Classification of Gastritis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>Acute Gastritis</td>
</tr>
<tr>
<td>Hemorrhagic/erosive gastritis</td>
</tr>
<tr>
<td>Helicobacter gastritis</td>
</tr>
<tr>
<td>Chronic Gastritis</td>
</tr>
<tr>
<td>Non-atrophic</td>
</tr>
<tr>
<td>Atrophic</td>
</tr>
<tr>
<td>Chemical</td>
</tr>
<tr>
<td>Radiation</td>
</tr>
<tr>
<td>Lymphocytic</td>
</tr>
<tr>
<td>Eosinophilic</td>
</tr>
<tr>
<td>Non-infectious granulomatous</td>
</tr>
<tr>
<td>Other infectious gastritides</td>
</tr>
</tbody>
</table>

*Most common causes
Clinical Features
- non-erosive gastritis is asymptomatic (except in certain rare causes like Crohn's disease); difficult to diagnose clinically or endoscopically – requires biopsy for diagnosis
- erosive gastritis can cause bleeding (pain only if progresses to ulcers – rare); can be seen endoscopically

Treatment
- determined by etiology (see H. pylori, G13, NSAID, G14 and Stress-Induced Ulceration, G14)
- non-pharmacological: avoidance of mucosal irritants such as alcohol, NSAIDs, and foods that trigger symptoms

Peptic Ulcer Disease

Definition
- focal defects in the mucosa that penetrate the muscularis mucosal layer results in scarring (defects superficial to the muscularis mucosa have erosions and no scarring)
- peptic ulcer disease includes defects located in the stomach (gastric ulcers) and duodenum (duodenal ulcers)

Etiology

Table 6. Etiology of Peptic Ulcer Disease

<table>
<thead>
<tr>
<th></th>
<th>Duodenal</th>
<th>Gastric</th>
</tr>
</thead>
<tbody>
<tr>
<td>H. pylori infection</td>
<td>90%</td>
<td>60%</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>7%</td>
<td>35%</td>
</tr>
<tr>
<td>Physiologic stress-induced</td>
<td>&lt;3%</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>Zollinger-Ellison (ZE) syndrome</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Idiopathic</td>
<td>15%</td>
<td>10%</td>
</tr>
</tbody>
</table>

- NSAID negative, H. pylori negative ulcers becoming more commonly recognized
- others: CMV, ischemic, idiopathic
- alcohol: damages gastric mucosa but rarely causes ulcers
- peptic ulcer associated with tobacco, cirrhosis of liver, COPD, and chronic renal failure

Clinical Features
- dyspepsia: most common presenting symptom
  - only 5% of patients with dyspepsia have ulcers, while most have functional disease
- may present with complications
  - bleeding 10% (severe if from gastroduodenal artery)
  - perforation 2% (usually anterior ulcers)
  - gastric outlet obstruction 2%
  - penetration (posterior) 2%; may also cause pancreatitis
- duodenal ulcers: 6 classical features, but history alone cannot distinguish from functional dyspepsia
  - epigastric pain; may localize to tip of xiphoid
  - burning
  - develops 1-3 h after meals
  - relieved by eating and antacids
  - interrupts sleep
  - periodicity (tends to occur in clusters over wk with subsequent periods of remission)
- gastric ulcers: more atypical symptoms; a biopsy is necessary to exclude malignancy

Investigations
- endoscopy (most accurate)
- upper GI series
- H. pylori tests (see Table 7)
- fasting serum gastrin measurement if Zollinger-Ellison (ZE) syndrome suspected

Treatment
- specific management depends on etiology; (see H. pylori, G13, NSAID-Induced Ulceration, G14 and Stress-Induced Ulceration, G14)
- eradicate H. pylori if present; chief advantage of triple therapy over PPI is to lower ulcer recurrence rate
- stop NSAIDs if possible
- start PPI: inhibits parietal cell H+/K⁺-ATPase pump which secretes acid
  - heals most ulcers, even if NSAIDs are continued
- other medications (e.g. histamine H₂-antagonists) less effective
- discontinue tobacco
- no diet modifications required but some people have fewer symptoms if they avoid caffeine, alcohol, and spices

Gastric vs. Duodenal Ulcers
Gastric ulcers must always be biopsied to rule out malignancies; duodenal ulcers are rarely malignant
Management of Bleeding Peptic Ulcers
- OGD to explore upper GI tract
- IV pantoprazole continuous drip
- establish risk of rebleeding/continuous bleed (since most ulcers stop bleeding spontaneously)
  - clinical risk factors: increased age (>60), bleeding diathesis, history of PUD, comorbid disease, hemodynamically unstable
  - endoscopic signs of recurrent bleeding (active bleeding, visible vessel, clot, red spot) more predictive than clinical risk factors
  - if high risk, consider ICU admission

Figure 6. Approach to management of suspected bleeding peptic ulcer
Adapted from: Gralnek I, Barkun A, Bardou M. Management of acute bleeding from a peptic ulcer. NEJM 2008;359:928-937

H. pylori-Induced Peptic Ulceration

Pathophysiology
- H. pylori: Gram-negative flagellated rod that resides on but does not invade the gastric mucosa
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- acid secreted by parietal cells (stimulated by vagal acetylcholine, gastrin, histamine) necessary for most ulcers
- theories of how H. pylori causes ulcers: none satisfactory, but pattern of colonization correlates with outcome
  - gastritis only in antrum (15% of patients), high gastric acid, associated with duodenal ulcer, may progress to gastric metaplasia of duodenum where ulcer forms
  - gastritis throughout stomach (“pangastritis” – 85% of patients), low gastric acid, associated with stomach ulcer and cancer

Epidemiology
- H. pylori is found in about 20% of all Canadians
  - highest prevalence in those raised during 1930s
  - infection most commonly acquired in childhood, presumably by fecal-oral route
  - high prevalence in developing countries, low socioeconomic status (poor sanitation and overcrowding)

Outcome
- gastritis (non-erosive) in 100% of patients but asymptomatic
- peptic ulcer in 15% of patients
- gastric malignancy (gastric carcinoma and mucosal associated lymphomatous tissue [MALT] lymphoma in 0.5% of patients)
- most are asymptomatic but still worthwhile eradicating to lower future risk of peptic ulcer/ gastric malignancy and prevent spread to others (mostly children <5 yr of age)
Diagnosis

Table 7. Diagnosis of *H. pylori* Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-invasive Tests</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urea breath test</td>
<td>90-100%</td>
<td>89-99%</td>
<td>Affected by PPI therapy (false negatives)</td>
</tr>
<tr>
<td>Serology</td>
<td>88-99%</td>
<td>89-95%</td>
<td>Can remain positive after treatment</td>
</tr>
<tr>
<td><strong>Invasive Tests (require endoscopy)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>93-99%</td>
<td>95-99%</td>
<td>Gold standard; affected by PPI therapy (false negatives)</td>
</tr>
<tr>
<td>Rapid urease test (on biopsy)</td>
<td>89-98%</td>
<td>93-100%</td>
<td>Rapid</td>
</tr>
<tr>
<td>Microbiology culture</td>
<td>98%</td>
<td>95-100%</td>
<td>Research only</td>
</tr>
</tbody>
</table>

Treatment: *H. pylori* Eradication

- **triple therapy for 7-14 d (Hp-Pac™):** PPI bid (e.g. lansoprazole 30 mg bid) + amoxicillin 1 g bid + clarithromycin 500 mg bid
  - 80% success rate
- **quadruple therapy for 10-14 d:** PPI bid + bismuth 525 mg qid + tetracycline 500 mg qid + metronidazole 250 mg qid
  - only recommended as first line therapy if resistance to clarithromycin or metronidazole is high, or in patients with recent or repeated exposure to these drugs
  - levofloxacin can replace metronidazole or tetracycline
- **sequential therapy**
  - days 1-5: PPI bid + amoxicillin 1 g bid
  - days 6-10: PPI bid + clarithromycin 500 mg bid + tinidazole (generally substitute with metronidazole as tinidazole not available in Canada) 500 mg bid
  - 5-15% of cases are resistant to all known therapies

### NSAID-Induced Ulceration

- NSAID use causes gastric mucosal petechiae in virtually all, erosions in most, ulcers in some (25%)
  - erosions bleed, but usually only ulcers cause significant clinical problems
- most NSAID ulcers are clinically silent: dyspepsia is as common in patients with ulcers as in patients without ulcers; NSAID-induced ulcers characteristically present with complications (bleeding, perforation, obstruction)
- NSAIDs more commonly cause gastric ulcers than duodenal ulcers
- may exacerbate underlying duodenal ulcer disease

Pathophysiology

- direct: erosions/petechiae – are due to local (direct) effect of drug on gastric mucosa
- indirect: systemic NSAID effect (intravenous NSAID causes ulcers, but not erosions), inhibits mucosal cyclooxygenase, leading to decreased synthesis of protective prostaglandins, thus leading to ulcers

### Risk Factors For NSAID Causing Peptic Ulcer

- previous peptic ulcers/UGIB
- age
- high dose of NSAID/multiple NSAIDs being taken
- concomitant corticosteroid use
- concomitant cardiovascular disease/other significant diseases

Treatment

- prophylactic cytoprotective therapy with a PPI is recommended if any of the above risk factors exist concomitantly with ASA/NSAID use
- lower NSAID dose or stop all together and replace with acetaminophen
- combine NSAID with PPI or misoprostol in one tablet
- enteric coating of Aspirin* (ECASA) provides minor benefit since this decreases incidence of erosion, not incidence of ulceration

### Stress-Induced Ulceration

Definition

- ulceration or erosion in the upper GI tract of ill patients, usually in ICU
- lesions most commonly in fundus of stomach

Pathophysiology

- unclear: likely involves ischemia; may be caused by CNS disease, acid hypersecretion, Cushing ulcers
- physiological stress (e.g. fever, severe illness, complex post-operative course) causes ulcers and erosions

If at high risk for development of ulcers, prophylaxis with PPI indicated
Gastroenterology Stomach and Duodenum/Small and Large Bowel

Toronto Notes 2016

Risk Factors
- mechanical ventilation
- anti-coagulation
- multi-organ failure
- sepsis
- severe surgery/trauma
- CNS injury ("Cushing's ulcers")
- burns involving more than 35% of body surface

Clinical Features
- UGIB (see Upper Gastrointestinal Bleeding, G25)
- painless

Treatment
- prophylaxis with gastric acid suppressants (H2-blockers or PPI) decreases risk of UGIB, but may increase risk of pneumonia
- treatment same as for bleeding peptic ulcer but often less successful

Gastric Carcinoma
- see General Surgery, GS19

Small and Large Bowel

Classification of Diarrhea

Definition
- clinically: diarrhea defined as stools that are looser and/or more frequent than normal; physiologically: 24 h stool weight >200 g (less useful clinically)

Classification
- acute vs. chronic
- small volume (tablespoons of stool; typical of colonic diseases) vs. large volume (>1/2 cup stool; typical of small bowel diseases)
- watery vs. steatorrhea
- secretory (diarrhea persists with fasting) vs. osmotic (diarrhea stops with fasting)

Acute Diarrhea

Definition
- passage of frequent unformed stools for <14 d

Etiology
- most commonly due to infections
- most infections are self-limiting and resolve within 7 d

Risk Factors
- food (seafood, chicken, turkey, eggs, beef)
- medications: antibiotics, laxatives
- others: high risk sexual activity, infectious outbreaks, family history (IBD)

Table 8. Classification of Acute Diarrhea

<table>
<thead>
<tr>
<th>Definition</th>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td>Usually colon</td>
<td>Usually small intestine</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Organisms and cytotoxins invade mucosa, killing mucosal cells, and further perpetuating the diarrhea</td>
<td>Stimulation of intestinal water secretion and inhibition of water absorption (i.e. secretory problem)</td>
</tr>
<tr>
<td>Sigmoidoscopy</td>
<td>Usually abnormal mucosa seen</td>
<td>Usually normal</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Bloody (not always)</td>
<td>Watery, little or no blood</td>
</tr>
<tr>
<td></td>
<td>Small volume, high frequency</td>
<td>Large volume</td>
</tr>
<tr>
<td></td>
<td>Often lower abdominal cramping with urgency ± tenesmus</td>
<td>Upper/periumbilical pain/cramp ± shock</td>
</tr>
<tr>
<td></td>
<td>May have fever ± shock</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>Fecal WBC and RBC positive</td>
<td>Fecal WBC negative</td>
</tr>
<tr>
<td>Etiology</td>
<td>See Differential Diagnosis of Presenting Complaints, G4</td>
<td>See Differential Diagnosis of Presenting Complaints, G4</td>
</tr>
<tr>
<td>Differential Diagnosis</td>
<td>Acute presentation of idiopathic inflammatory bowel disease</td>
<td>Acute presentation of non-inflammatory chronic diarrhea (e.g. celiac disease)</td>
</tr>
<tr>
<td>Significance</td>
<td>Higher yield with stool C&amp;S</td>
<td>Lower yield with stool C&amp;S</td>
</tr>
<tr>
<td></td>
<td>Can progress to life-threatening megacolon, perforation, hemorrhage</td>
<td>Chief life-threatening problem is electrolyte disturbances/ fluid depletion</td>
</tr>
<tr>
<td></td>
<td>Antibiotics may benefit</td>
<td>Antibiotics unlikely to be helpful</td>
</tr>
</tbody>
</table>

Infectious Causes of Inflammatory Diarrhea
- Yersinia
- Shigella
- Salmonella
- E. coli (EHEC O157:H7), E. histolytica
- Campylobacter, C. difficile

Useful Questions in Acute Diarrhea
- Those Fads Wilt
  - Travel
  - Homosexual contacts
  - Outbreaks
  - Seafood
  - Extra-intestinal signs of IBD
  - Family history
  - Antibiotics
  - Diet
  - Steatorrhea
  - Weight loss
  - Immunosuppressed
  - Laxatives
  - Tumour history

Stool Osmotic Gap
- Stool osmolality is normally about 290 mOsm/kg and can be approximated by the calculated stool osmolality
  \[2 \times [\text{Na}^+]_{\text{stool}} + [\text{K}^+]_{\text{stool}}\]
- In osmotic diarrhea, measured stool osmolality > calculated stool osmolality
- In secretory diarrhea measured stool osmolality = calculated stool osmolality

Curling’s and Cushing’s Ulcers
- Curling’s ulcer: acute peptic ulcer of the duodenum resulting as a complication from severe burns when reduced plasma volume leads to ischemia and cell necrosis (sloughing) of the gastric mucosa (think BURN from a CURLing iron)
- Cushing’s ulcer: peptic ulcer produced by elevated intracranial pressure (may be due to stimulation of vagal nuclei secondary to elevated ICP which leads to increased secretion of gastric acid)
Investigations

- stool cultures/microscopy (C&S/O&P) are required only if diarrhea is inflammatory, severe, or for epidemiological purposes (day care worker, nursing home resident, community outbreaks, e.g. Walkerton, etc.)
  - C&S only tests Campylobacter, Salmonella, Shigella, E. coli
  - other organisms must be ordered separately
- flexible sigmoidoscopy (without bowel preparation): useful if inflammatory diarrhea suspected
  - biopsies are the most useful method of distinguishing idiopathic IBD (Crohn's disease and ulcerative colitis) from infectious colitis or acute self-limited colitis
- C. difficile toxin: indicated when recent/remote antibiotic use, hospitalization, nursing home, or recent chemotherapy

Treatment

- fluid and electrolyte replacement orally in most cases, intravenous if severe extremes of age/coma
- anti-diarrheals
  - antimitoty agents: diphenoxylate, loperamide (Imodium®); contraindicated in mucosal inflammation
    - side effects: abdominal cramps, toxic megacolon
  - absorbants: kaolin/pectin (Kaopectate®), methylcellulose, activated attapulgite
    - act by absorbing intestinal toxins/micro-organisms, or by coating intestinal mucosa
    - much less effective than antimitoty agents
  - modifiers of fluid transport: bismuth subsalicylate (Pepto-Bismol®) may be helpful (but should not be used in the presence of bloody diarrhea or fever)
- antibiotics: rarely indicated
  - risks
    - prolonged excretion of enteric pathogen (especially Salmonella)
    - drug side effects (including C. difficile infection)
    - development of resistant strains
    - renal failure/hemolysis (enterohemorrhagic E. coli O157:H7)
  - indications for antimicrobial agents in acute diarrhea
    - septicemia
    - prolonged fever with fecal blood or leukocytes
  - clearly indicated: Shigella, V. cholerae, C. difficile, traveller's diarrhea (enterotoxigenic E. coli [ETEC]), Giardia, Entamoeba histolytica, Cyclospora
  - situational: Salmonella, Campylobacter, Yersinia, non-enterotoxigenic E. coli
  - Salmonella: always treat Salmonella typhi (typhoid or enteric fever); treat other Salmonella only if there is underlying immunodeficiency, hemolytic anemia, extremes of age, aneurysms, prosthetic valve grafts/joints, sickle cell disease

Chronic Diarrhea

Definition
- passage of frequent unformed stool for >14 d
- approach is similar to that of acute diarrhea except that the majority of cases are non-infectious

Etiology/Classification
- see Differential Diagnosis of Common Presenting Complaints, G4

Investigations

- guided by history
- stool analysis for: C. difficile toxin, C&S, O&P ± fecal fat, WBC
- blood for: CBC, electrolytes, CRP, TSH, celiac serology (IgA anti-tTG; ask for serum protein electrophoresis or immunoglobulin quantitation to rule out IgA deficiency which has an increased frequency in celiac disease)
- colonoscopy and ileoscopy with biopsy
- upper GI endoscopy with duodenal biopsy
- wireless small bowel endoscopy capsule (low yield)
- trial of lactose free diet
  - caveat: may delay diagnosis of IBD and celiac disease

Traveller’s Diarrhea

- see Infectious Diseases, ID13

Finally: A Role for Bacteriotherapy
Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile
NEJM 2013; 368:407-15

For centuries, out-of-the-box thinkers have speculated that the colonic bacteria all of us have, but which differs among individuals, play a role in disease. More recently, the colonic microbiome has become the hottest area of research in gastroenterology. The best documented medical indication for manipulating the colonic bacteria is recurrent C. difficile infection. In this randomized study of this disease, infusion of donor feces via a nasoduodenal tube resolved diarrhea in 81% of patients, without side-effects, compared to 31% given the standard treatment of oral vancomycin, and 23% of patients given oral vancomycin plus bowel lavage. It takes little prescience to predict an onslaught of future studies investigating the therapeutic potential of altering the human microbiome.
Maldigestion and Malabsorption

Definition
- **maldigestion**: inability to break down large molecules in the lumen of the intestine into their component small molecules
- **malabsorption**: inability to transport molecules across the intestinal mucosa into circulation
- **malassimilation**: encompasses both maldigestion and malabsorption

Etiology
- **maldigestion**
  - inadequate mixing of food with enzymes (e.g. post-gastrectomy)
  - pancreatic exocrine deficiency
  - primary diseases of the pancreas (e.g. cystic fibrosis, pancreatitis, cancer)
  - bile salt deficiency
    - terminal ileal disease (impairment recycling), bacterial overgrowth (deconjugation of bile salts), rarely liver disease (cholestatic, e.g. primary biliary cirrhosis)
  - specific enzyme deficiencies (e.g. lactase)
- **malabsorption**
  - inadequate absorptive surface
  - infections/infestations (e.g. Whipple's disease, Giardia)
  - immunologic or allergic injury (e.g. celiac disease)
  - infiltration (e.g. lymphoma, amyloidosis)
  - fibrosis (e.g. systemic sclerosis, radiation enteritis)
  - bowel resection (length, site, location, presence/absence of ileocecal valve are important)
  - extensive ileal Crohn's disease
  - drug-induced
    - cholestyramine, ethanol, neomycin, tetracycline, and other antibiotics
  - endocrine
  - DM (complex pathogenesis)

Clinical Features
- symptoms usually vague unless disease is severe
- weight loss, diarrhea, steatorrhea, weakness, fatigue
- manifestations of malabsorption/deficiency

Table 9. Absorption of Nutrients and Fat Soluble Vitamins

<table>
<thead>
<tr>
<th>Deficiency</th>
<th>Absorption</th>
<th>Clinical Disease and/or Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td>Duodenum, upper jejunum</td>
<td>Hypochromic, microcytic anemia, glossitis, koilonychia (spoon nails, pica)</td>
<td>↓ Hb, ↓ serum Fe, ↓ serum ferritin</td>
</tr>
<tr>
<td>Calcium</td>
<td>Duodenum, upper jejunum (binds to Ca^{2+} complex-protein in cells; levels increased by Vit D)</td>
<td>Metabolic bone disease, may get tetany and paresthesias if serum calcium falls (see Endocrinology, E37)</td>
<td>↓ serum Ca^{2+}, ↓ serum Mg^{2+}, and ↑ ALP Evaluate for ↓ bone mineralization radiographically (DEXA)</td>
</tr>
<tr>
<td>Folic Acid</td>
<td>Jejunum</td>
<td>Megaloblastic anemia, glossitis, ↓ red cell folate (may see ↑ folic acid with bacterial overgrowth)</td>
<td>↓ serum folic acid</td>
</tr>
<tr>
<td>Vitamin B_{12}</td>
<td>B_{12} ingested and bound to R proteins mainly from salivary glands; stomach secretes intrinsic factor (IF) in acidic medium; in basic medium, proteases from the pancreas cleave R protein and B_{12}-IF complex forms, protecting B_{12} from further protease attack; B_{12} absorbed in ileum and binds to transcobalamin (TC)</td>
<td>Subacute combined degeneration of the spinal cord, peripheral optic neuropathy, dementia, megaloblastic anemia, glossitis</td>
<td>Differentiate causes by nuclear Schilling test (when available) Positive anti-intrinsic factor antibodies and atrophic gastritis point toward pernicious anemia (see Hematology, H24)</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>Complex polysaccharides hydrolyzed to oligosaccharides, and disaccharides by salivary and pancreatic enzymes Monosaccharides absorbed in duodenum/jejunum</td>
<td>Generalized malnutrition, weight loss, flatus, and diarrhea</td>
<td>Hydrogen breath test Trial of carbohydrate-restricted diet D-xylene test</td>
</tr>
<tr>
<td>Protein</td>
<td>Digestion at stomach, brush border, and inside cell Absorption occurs primarily in the jejunum</td>
<td>General malnutrition and weight loss, anemia, and ↓ libido if severe</td>
<td>↓ serum albumin (low sensitivity)</td>
</tr>
<tr>
<td>Fat</td>
<td>Lipase, colipase, phospholipase A (pancreatic enzymes), and bile salts needed for digestion Products of lipolysis form micelles which solubilize fat and aid in absorption Fatty acids diffuse into cell cytoplasm</td>
<td>Generalized malnutrition, weight loss, and diarrhea Foul-smelling feces + gas Steatorrhea</td>
<td>Small bowel biopsy MRCP, ERCP, pancreatic function tests (not routinely available) Quantitative stool fat test (72 h) May start with qualitative stool fat test (Sudan stain of stool) C-triolein breath test (not routinely available)</td>
</tr>
<tr>
<td>Vitamin A</td>
<td>Dietary sources (e.g. milk, eggs, liver, carrots, sweet potatoes)</td>
<td>Night blindness Dry skin Keratomalacia</td>
<td></td>
</tr>
<tr>
<td>Vitamin D</td>
<td>Skin (via UV light) or diet (e.g. eggs, fish oil, fortified milk)</td>
<td>Osteomalacia in adults Rickets in children</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Dietary sources (e.g. vegetable oils, nuts, leafy green vegetables)</td>
<td>Retinopathy, neurological problems</td>
<td></td>
</tr>
<tr>
<td>Vitamin K</td>
<td>Synthesized by intestinal flora</td>
<td>↑ risk of deficiency after prolonged use of broad spectrum antibiotics and/or starvation Prolonged INR may cause bleeding</td>
<td></td>
</tr>
</tbody>
</table>

Fat Soluble Vitamins: ADEK
- vitamin A, vitamin D, vitamin E, vitamin K

* Calcium malabsorption more commonly causes decreased bone density rather than hypocalcemia because serum calcium levels are protected by leaching calcium from the bone
Investigations
- transglutaminase antibody serology/immunoglobulin quantitation and abdominal imaging are most useful because celiac disease and chronic pancreatitis are the two most common causes of steatorrhea
- 72 h stool collection (weight, fat content) documents steatorrhea (gold standard)
- fecal elastase (not routinely available) to screen for pancreatic insufficiency and/or consider empiric trial of pancreatic enzymes based on clinical context
- serum carotene (precursor to vitamin A), folate, Ca\(^{2+}\), Mg\(^{2+}\), vitamin B\(_{12}\), albumin, ferritin, serum iron solution, INR/PTT
- stool fat globules on fecal smear stained with Sudan (rarely used)
- other tests specific for etiology (e.g. CT scan/MRI to visualize pancreas)

Treatment
- dependent on underlying etiology

Celiac Disease (Gluten Enteropathy/Sprue)

Definition
- abnormal small intestine mucosa due to intestinal reaction to gliadin, a component of gluten found in cereal grains

Etiology
- only autoimmune disease in which antigen (a peptide in α-gliadin) is recognized
- associated with other autoimmune diseases, especially Sjögren's, thyroid disease
- gluten, a protein in cereal grains, is broken down to gliadin, which is the toxic factor
- HLA-DQ2 (chromosome 6) found in 80-90% of patients compared with 20% in general population; celiac also associated with HLA-DQ8 (note: up to 40% of Caucasians carry the HLA alleles, but will never develop celiac disease)

Epidemiology
- more common in women
- family history: 10-15% of first-degree relatives
- may present any time from infancy (when cereals introduced) to elderly
- peak presentation in infancy

Clinical Features
- classic presentation: diarrhea, weight loss, anemia, symptoms of vitamin/mineral deficiency, failure to thrive; more common current presentation: bloating, gas, iron deficiency
- improves with gluten-free diet, deteriorates when gluten reintroduced
- disease is usually most severe in proximal bowel
  - thus iron, calcium, and folic acid deficiency (proximal absorption) more common than vitamin B\(_{12}\) deficiency (absorbed in ileum)
- gluten enteropathy may be associated with dermatitis herpetiformis skin eruption, epilepsy, myopathy, depression, paranoia, infertility, bone fractures/metabolic bone disease

Investigations
- small bowel mucosal biopsy (usually duodenum) is diagnostic with
  - increased intraepithelial lymphocytes (earliest pathologic finding)
  - crypt hyperplasia
  - villous atrophy
  - note: villous atrophy also seen in small bowel overgrowth, Crohn's, lymphoma, Giardia, HIV
- consider CT enterography to visualize small bowel to rule out lymphoma
- evidence of malabsorption (localized or generalized)
  - steatorrhea
  - low levels of ferritin/iron saturation, Ca\(^{2+}\), Fe, albumin, cholesterol, carotene, B\(_{12}\) absorption
- improvement with a gluten-free diet; should not be started before anti-tTG and biopsy
- serological tests
  - serum anti-tTG antibody, IgA, is 90-98% sensitive, 94-97% specific
  - IgA deficient patients have false-negative anti-tTG
    - therefore, measure serum IgA concomitantly (via serum quantitative protein electrophoresis)
- fecal fat >7%

Treatment
- dietary counseling
  - gluten free diet; avoid barley, rye, wheat (as these grains are related and also have toxic factor, similar to gliadin)
  - oats allowed if not contaminated by other grains (grown in soil without cross-contamination)
  - rice and corn flour are acceptable
  - iron, folate supplementation (with supplementation of other vitamins as needed)
if poor response to diet change, consider
  • alternate diagnosis
  • non-adherence to gluten-free diet
  • concurrent disease (e.g. microscopic colitis, pancreatic insufficiency)
  • development of intestinal (enteropathy-associated T-cell) lymphoma (abdominal pain,
  weight loss, palpable mass)
  • development of diffuse intestinal ulceration, characterized by aberrant intraepithelial T-cell
  population (precursor to lymphoma)

**Prognosis**
• associated with increased risk of lymphoma, carcinoma (e.g. small bowel and colon; slight
increase compared with general population), autoimmune diseases
• risk of lymphoma may be lowered by dietary gluten restriction

**Inflammatory Bowel Disease**

**Definition**
• Crohn’s disease (CD), ulcerative colitis (UC), indeterminate colitis or IBD-unclassified (IBDU)

**Pathophysiology**
• poorly understood
• sustained response of the immune system, perhaps to enteric flora in a genetically predisposed
individual
• current hypothesis: lack of appropriate down-regulation of immune responsiveness

**Genetics**
• increased risk of both UC and CD in relatives of patients with either disease, especially siblings,
early onset disease
  • familial risk greater if proband has CD rather than UC
• likely polygenomic pattern: 9 gene loci are associated
• CARD15/NOD2 gene mutation associated with CD (relative risk in heterozygote is 3, in
homozygote is 40), especially Ashkenazi Jews, early onset disease, ileal involvement, fistulizing
and stenotic disease
  • CARD15 gene product modulates NFκB, which is required for the innate immune response
to microbial pathogens, best expressed in monocytes-macrophages

**Clinical Features**

<table>
<thead>
<tr>
<th></th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location</strong></td>
<td>Any part of GI tract</td>
<td>Isolated to large bowel</td>
</tr>
<tr>
<td></td>
<td>• Small bowel + colon: 50%</td>
<td>Always involves rectum, may progress proximally</td>
</tr>
<tr>
<td></td>
<td>• Small bowel only: 30%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Colon only: 20%</td>
<td></td>
</tr>
<tr>
<td><strong>Rectal Bleeding</strong></td>
<td>Uncommon</td>
<td>Very common (80%)</td>
</tr>
<tr>
<td><strong>Diarrhea</strong></td>
<td>Less prevalent</td>
<td>Frequent small stools</td>
</tr>
<tr>
<td><strong>Abdominal Pain</strong></td>
<td>Post-prandial/colicky</td>
<td>Less common</td>
</tr>
<tr>
<td><strong>Fever</strong></td>
<td>Common</td>
<td>Uncommon</td>
</tr>
<tr>
<td><strong>Urgency/Tenesmus</strong></td>
<td>Uncommon (unless rectum involved)</td>
<td>Common</td>
</tr>
<tr>
<td><strong>Palpable Mass</strong></td>
<td>Frequent (25%), RLQ</td>
<td>Rare (if present, often related to cecum full of stool)</td>
</tr>
<tr>
<td><strong>Recurrence After Surgery</strong></td>
<td>Common</td>
<td>None post-colectomy</td>
</tr>
<tr>
<td><strong>Endoscopic Features</strong></td>
<td>Ulcers (aphthous, stellate, linear), patchy lesions, pseudopolyps, cobblestoning</td>
<td>Continuous diffuse inflammation, erythema, friability, loss of normal vascular pattern, pseudopolyps</td>
</tr>
<tr>
<td><strong>Histologic Features</strong></td>
<td>Transmural distribution with skip lesions, Focal inflammation ± noncaseating granulomas, deep fissuring + aphthous ulcerations, strictures, Glands intact</td>
<td>Mucosal distribution, continuous disease (no skip lesions), Architectural distortion, gland disruption, crypt abscess, Granulomas absent</td>
</tr>
<tr>
<td><strong>Radiologic Features</strong></td>
<td>Cobblestone mucosa, Frequent strictures and fistulae, AXR: bowel wall thickening &quot;string sign&quot;</td>
<td>Lack of haustra, Strictures rare; need to rule out complicating cancer</td>
</tr>
<tr>
<td><strong>Complications</strong></td>
<td>Strictures, fistulae, perianal disease</td>
<td>Toxic megacolon</td>
</tr>
<tr>
<td><strong>Colon Cancer Risk</strong></td>
<td>Increased if &gt;30% of colon involved</td>
<td>Increased except in proctitis</td>
</tr>
</tbody>
</table>
### Table 11. Extraintestinal Manifestations (EIM) of IBD

<table>
<thead>
<tr>
<th>System</th>
<th>Crohn’s Disease</th>
<th>Ulcerative Colitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythema nodosum</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Pyoderma gangrenosum</td>
<td>10%</td>
<td>Less common</td>
</tr>
<tr>
<td>Perianal skin tags</td>
<td>75-90%</td>
<td>Rare</td>
</tr>
<tr>
<td>Oral mucosal lesions</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>Statistically associated in 5-10% of those with IBD but not an EIM</td>
<td></td>
</tr>
<tr>
<td><strong>Rheumatologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral arthritis</td>
<td>15-20% of those with IBD (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>10% of those with IBD (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Sacroilitis</td>
<td>Occurs equally in CD and UC</td>
<td></td>
</tr>
<tr>
<td><strong>Ocular</strong> (1-10% of IBD)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uveitis (vision threatening)</td>
<td>3-4% of IBD patients (CD&gt;UC)</td>
<td></td>
</tr>
<tr>
<td>Episcrletis (benign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hepatobiliary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>15-35% of patients with ileal Crohn’s</td>
<td></td>
</tr>
<tr>
<td>PSC</td>
<td>1-5% of IBD cases involving colon</td>
<td></td>
</tr>
<tr>
<td>Fatty liver</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Urologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calculi</td>
<td>Most common in CD, especially following ileal resection</td>
<td></td>
</tr>
<tr>
<td>Ureteric obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fistulae</td>
<td>Characteristic of Crohn’s</td>
<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thromboembolism</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vasculitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin deficiencies (B12, Vit ADEK)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiopulmonary disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pancreatitis (rare)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Crohn’s Disease

**Definition**
- chronic transmural inflammatory disorder potentially affecting the entire gut from mouth to perianal region (“gum to bum”)

**Epidemiology**
- incidence 1-6/100,000; prevalence 10-100/100,000
- bimodal: onset before 30 yr, second smaller peak age 60; M=F
- incidence of Crohn’s increasing (relative to UC) especially in young females
- more common in Caucasians, Ashkenazi Jews
  - risk in Asians increases with move to Western countries
- smoking incidence in Crohn’s patients is higher than general population

**Pathology**
- most common location: ileum + ascending colon
- linear ulcers leading to mucosal islands and "cobblestone" appearance
- granulomas are found in 50% of surgical specimens, 15% of mucosal biopsies

**Clinical Features**
- natural history unpredictable; young age, perianal disease, and need for corticosteroids have been associated with poor prognosis, but associations are not strong enough to guide clinical decisions
- most often presents as recurrent episodes of abdominal cramps, diarrhea, and weight loss
- ileitis may present with post-prandial pain, vomiting, RLQ mass; mimics acute appendicitis
- extra-intestinal manifestations are more common with colonic involvement
- fistulae, fissures, abscesses are common
- deep fissures with risk of perforation into contiguous viscera (leads to fistulae and abscesses)
- enteric fistulae may communicate with skin, bladder, vagina, and other parts of bowel

**Investigations**
- colonoscopy with biopsy to visualize (less often gastroscopy)
- CT/MR enterography to visualize small bowel
- CRP elevated in most new cases, useful to monitor treatment response (especially acutely in UC)
- bacterial cultures, O&P, C. difficile toxin to exclude other causes of inflammatory diarrhea
Management (see Figure 7)

Table 12. Management of Crohn’s Disease

<table>
<thead>
<tr>
<th>Management</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle/Diet</td>
<td>Smoking cessation</td>
</tr>
<tr>
<td></td>
<td>Fluids only during acute exacerbation</td>
</tr>
<tr>
<td></td>
<td>Enteral diets may aid in remission only for Crohn’s ileitis, not colitis</td>
</tr>
<tr>
<td></td>
<td>No evidence for any non-enteral diet changing the natural history of Crohn’s disease, but may affect symptoms</td>
</tr>
<tr>
<td></td>
<td>Those with extensive small bowel involvement or extensive resection require electrolyte, mineral, and vitamin supplements (vit D, Ca²⁺, Mg²⁺, zinc, Fe, B₁₂)</td>
</tr>
<tr>
<td></td>
<td>CAUTION if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups</td>
</tr>
<tr>
<td>Antidiarrheal Agents*</td>
<td>Loperamide (Imodium®) &gt; diphenoxylate (Lomotil®) &gt; codeine (cheap but addictive)</td>
</tr>
<tr>
<td></td>
<td>All work by decreasing small bowel motility</td>
</tr>
<tr>
<td></td>
<td>CAUTION if colitis is severe (risk of precipitating toxic megacolon), therefore avoid during flare-ups</td>
</tr>
<tr>
<td>5-ASA</td>
<td>Efficacy controversial: most evidence for mild colonic disease</td>
</tr>
<tr>
<td></td>
<td>Sulfasalazine (Salazopyrin®): 5-ASA bound to sulfapyridine</td>
</tr>
<tr>
<td></td>
<td>Hydrolysis by intestinal bacteria releases 5-ASA (active component)</td>
</tr>
<tr>
<td></td>
<td>Dose-dependent efficacy</td>
</tr>
<tr>
<td></td>
<td>Mesalamine (Pentasa®): coated 5-ASA releases 5-ASA in the ileum and colon</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>e.g. metronidazole (20 mg/kg/d, bid or tid dosing) or ciprofloxacin</td>
</tr>
<tr>
<td></td>
<td>Best described for perianal Crohn’s, although characteristically relapse when discontinued</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Prednisone: starting dose 40 mg OD for acute exacerbations; IV methylprednisolone if severe</td>
</tr>
<tr>
<td></td>
<td>No proven role for steroids in maintaining remissions; masks intra-abdominal sepsis</td>
</tr>
<tr>
<td>Immunosuppressives</td>
<td>6-mercaptopurine (6-MP), azathioprine (Imuran®); methotrexate (used less often)</td>
</tr>
<tr>
<td></td>
<td>More often used to maintain remission than to treat active inflammation</td>
</tr>
<tr>
<td></td>
<td>Most commonly used as steroid-sparing agents</td>
</tr>
<tr>
<td></td>
<td>i.e. to lower risk of relapse as corticosteroids are withdrawn</td>
</tr>
<tr>
<td></td>
<td>May require &gt; 3 mo to have beneficial effect; usually continued for several years</td>
</tr>
<tr>
<td></td>
<td>May help to heal fistulae, decrease disease activity</td>
</tr>
<tr>
<td></td>
<td>Side effects: vomiting, pancreatitis, bone marrow suppression, increased risk of malignancy</td>
</tr>
<tr>
<td>Biologics</td>
<td>Infliximab IV (Remicade®) or adalimumab SC (Humira®): both = antibody to TNF-α</td>
</tr>
<tr>
<td></td>
<td>Proven effective for treatment of fistulae and patients with medically refractory CD</td>
</tr>
<tr>
<td></td>
<td>First-line immunosuppressive therapy with infliximab + azathioprine more effective than using either alone</td>
</tr>
<tr>
<td>Surgical/Experimental</td>
<td>Surgical treatment (see General Surgery, GS29)</td>
</tr>
<tr>
<td></td>
<td>Surgery generally reserved for complications such as fistulae, obstruction, abscess, perforation, bleeding, and for medically refractory disease</td>
</tr>
<tr>
<td></td>
<td>If &lt; 50% or &lt; 200 cm of functional small intestine, risk of short bowel syndrome</td>
</tr>
<tr>
<td></td>
<td>At least 50% clinical recurrence within 5 yr; 85% within 15 yr; endoscopic recurrence rate even higher</td>
</tr>
<tr>
<td></td>
<td>40% likelihood of second bowel resection; 30% likelihood of third bowel resection</td>
</tr>
<tr>
<td></td>
<td>Complications of ileal resection</td>
</tr>
<tr>
<td></td>
<td>&lt; 100 cm resected → watery diarrhea or choleraema (impair bile salt absorption)</td>
</tr>
<tr>
<td></td>
<td>Treatment: cholestyramine or anti-diarrheals e.g. loperamide</td>
</tr>
<tr>
<td></td>
<td>&gt; 100 cm resected → steatorrhea (reduced mucosal surface area, bile salt deficiency)</td>
</tr>
<tr>
<td></td>
<td>Treatment: fat restriction, medium chain triglycerides</td>
</tr>
</tbody>
</table>

*Cholestyramine: a bile-salt binding resin; for watery diarrhea with < 100 cm of terminal ileum diseased or resected; however, non-specific anti-diarrheals are more convenient and often more potent

Prognosis
- highly variable course
- 10% disabled by the disease eventually, spontaneous remission also described
- increased mortality, especially with more proximal disease, greatest in the first 4-5 yr
- complications include
  - intestinal obstruction/perforation
  - fistula formation
  - malignancy (lower risk compared to UC)
- surveillance colonoscopy same as ulcerative colitis (see Ulcerative Colitis, G22) if more than 1/3 of colon involved

Traditional Medical Management of Crohn’s

<table>
<thead>
<tr>
<th>Induction of Remission</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-ASA</td>
<td>?</td>
</tr>
<tr>
<td>Steroids</td>
<td>+</td>
</tr>
<tr>
<td>Immunosuppressive</td>
<td>+</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>+</td>
</tr>
<tr>
<td>MTX</td>
<td>+</td>
</tr>
<tr>
<td>Infliximab</td>
<td>+</td>
</tr>
</tbody>
</table>

Note: Starting with immunosuppressives plus immunomodulators (‘bottom-up approach’) increasingly being used (Lancet 2008;371:660-667). Combination of azathioprine and infliximab has the highest remission rate yet described with medical treatment (AJG 2010;82;1383-1395). Characteristically more than 1 yr between onset of symptoms and diagnosis of Crohn’s disease.

Nutrition
- Symptomatic therapy (e.g. loperamide, acetaminophen)
- 5-ASA (mesalamine)
- Antibiotics (Flagyl™, Cipro™)
- Corticosteroids (e.g. budesonide, prednisone)
- Immunosuppression (e.g. azathioprine, 6-MP, methotrexate)
- Immunomodulators (e.g. TNF-antagonists: infliximab, adalimumab)

Experimental therapy or surgery

Figure 7. Traditional graded approach to induction therapy in Crohn’s disease
Ulcerative Colitis

Definition
• inflammatory disease affecting colonic mucosa anywhere from rectum (always involved) to cecum

Epidemiology
• incidence 2-10/100,000; prevalence 35-100/100,000 (more common than Crohn’s)
• 2/3 onset by age 30 (with second peak after 50); M:F
• small hereditary contribution (15% of cases have 1st degree relative with disease)
• risk is less in smokers
• inflammation limited to rectum or left colon is more common than pancolitis

Pathology
• disease can involve any portion of lower bowel ranging from rectum only (proctitis) to entire colon (pancolitis)
• inflammation is diffuse, continuous and confined to mucosa

Clinical Features
• rectal bleeding is the hallmark feature, however diarrhea may be present if more than the rectum is involved
  ▪ can also have abdominal cramps/pain, especially with defecation
• severity of colonic inflammation correlates with symptoms (stool volume, amount of blood in stool)
• tenesmus, urgency, incontinence
• systemic symptoms: fever, anorexia, weight loss, fatigue in severe cases
• extra-intestinal manifestations (see Table 11)
• characteristic exacerbations and remissions; 5% of cases are fulminant

Investigations
• sigmoidoscopy with mucosal biopsy (to exclude self-limited colitis) without bowel prep often sufficient for diagnosis
• colonoscopy helpful to determine extent of disease; contraindicated in severe exacerbation
  ▪ CT colonography (formerly barium enema) if colonoscopy cannot be done; contraindicated in severe disease
• stool culture, microscopy, C. difficile toxin assay necessary to exclude infection
  ▪ no single confirmatory test

Treatment
• mainstays of treatment: 5-ASA (mesalamine) derivatives (only in mild to moderate disease) and corticosteroids, with azathioprine used in steroid-dependent or resistant cases
• diet of little value in decreasing inflammation but may alleviate symptoms
• anti-diarrheal medications generally not indicated in UC
• 5-ASA
  ▪ topical (suppository or enema): very effective for distal disease (distal to splenic flexure), preferable to corticosteroids
  ▪ oral: effective for mild to moderate, but not severe colitis (e.g. sulfasalazine 3-4 g/d, mesalamine 4 g/d)
  ▪ commonly used in maintaining remission (decreases yearly relapse rate from 60% to 15%)
  ▪ may decrease rate of colorectal cancer
• corticosteroids
  ▪ to remit acute disease, especially if severe or first attack; may need maximum dose IV steroids initially (e.g. methylprednisolone 30 mg IV q12h)
  ▪ limited role as maintenance therapy for mild to moderate disease
  ▪ use suppositories for proctitis, enemas for proctosigmoiditis
  ▪ topical steroids (e.g. hydrocortisone foam, budesonide enemas) for inflammation distal to splenic flexure
• immunosuppressants (steroid-sparing)
  ▪ in hospitalized patients with severe UC – add IV infliximab if no response to IV methylprednisolone within 3 days; then colectomy if inadequate response to drugs or no response to corticosteroids + infliximab
  ▪ biologics (infliximab, adalimumab, golimumab) can also be used for outpatients with moderate-severe disease, particularly those that are steroid-unresponsive or steroid-dependent
  ▪ azathioprine and 6-mercaptopurine: too slow to rapidly resolve acute relapse
  ▪ most commonly used to maintain remission as corticosteroids withdrawn
• surgical treatment curative
  ▪ aim for cure with colectomy; bowel continuity can be restored with ileal pouch-anal anastomosis (IPAA)
• indications: failure of adequate medical therapy, toxic megacolon, uncontrollable bleeding, pre-cancerous changes detected either by endoscopy or endoscopic biopsies (dysplasia), inability to taper corticosteroids, overt malignancy
Complications
• similar to CD, except
  ▪ more liver problems (especially PSC in men)
  ▪ greater risk of colorectal cancer
  ▪ risk increases with duration and extent of disease (5% at 10 yr, 15% at 20 yr for pancolitis; overall relative risk is 8%)
  ▪ risk also increases with active mucosal inflammation and sclerosing cholangitis
  ▪ thus, regular colonoscopy and biopsy in pancolitis of ≥8 yr is indicated
  ▪ toxic megacolon (transverse colon diameter >6 cm on abdominal x-ray) with immediate danger of perforation (see General Surgery, GS30)

Prognosis
• chronic relapsing pattern in most patients
• 10-15% chronic continuous pattern
• >1 attack in almost all patients
• more colonic involvement in the 1st yr correlates with increased severity of attacks and increased colectomy rate
  ▪ colectomy rate = 1% for all patients after the 1st yr; 20-25% eventually undergo colectomy
• normal life expectancy
• if proctitis only, usually benign course

Irritable Bowel Syndrome
Definition
• a form of functional bowel disease; more than just a label for GI symptoms unexplained after normal investigations

Epidemiology
• 20% of North Americans
• onset of symptoms usually in young adulthood
• F>M

Pathophysiology
• associated with either abnormal perception of intestinal activity or abnormal intestinal motility
• abnormal motility: multiple abnormalities described; unclear if associations or if causative
• psychological: stress may increase IBS symptoms but does not cause IBS
• types of IBS: IBS with diarrhea, IBS with constipation, IBS-mixed type (both diarrhea and constipation)

Diagnosis

Table 13. Rome III Criteria for Diagnosing Irritable Bowel Syndrome

<table>
<thead>
<tr>
<th>IBS Rome III Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥12 wk in the past 12 mo of abdominal discomfort or pain that has 2 out of 3 features</td>
</tr>
<tr>
<td>• Relieved with defecation</td>
</tr>
<tr>
<td>• Associated with a change in frequency of stool</td>
</tr>
<tr>
<td>• Associated with a change in consistency of stool</td>
</tr>
<tr>
<td>The following are supportive, but not essential to the diagnosis:</td>
</tr>
<tr>
<td>• Abnormal stool frequency (≥3/d or &lt;3/wk)</td>
</tr>
<tr>
<td>• Abnormal stool form (lumpy/hard/loose/watery) ≥1/4 of defecations</td>
</tr>
<tr>
<td>• Abnormal stool passage (straining, urgency, feeling of incomplete evacuation) ≥1/4 of defecations</td>
</tr>
<tr>
<td>• Passage of mucus ≥1/4 of defecations</td>
</tr>
<tr>
<td>• Bloating</td>
</tr>
</tbody>
</table>

Diagnosis of IBS Less Likely in Presence of “Red Flag” Features

| Weight loss |
| Fever |
| Nocturnal defecation |
| Anemia |
| Blood or pus in stool |
| Abnormal gross findings on flexible sigmoidoscopy |

Investigations
• if history consistent with Rome III criteria, no alarm symptoms, and no family history of IBD or colorectal cancer, limited investigations required
• aim is to rule out diseases which mimic IBS, particularly celiac disease and IBD
• investigations can be limited to CBC, inflammatory markers (ESR, CRP) and celiac serology
• if available, fecal calprotectin is likely more reliable test to rule out IBD
• consider TSH, stool cultures depending on clinical circumstances
• consider colonoscopy (e.g. if alarming features present, family history of IBD or age > 50)

When Considering Complications of IBD, Think: ULCERATIVE COLITIS

| Urinary calculi |
| Liver problems |
| Cholelithiasis |
| Epithelial problems |
| Retardation of growth/sexual maturation |
| Arthritis |
| Thrombophlebitis |
| Iatrogenic complications |
| Vitamin deficiencies |
| Eyes |
| Colorectal cancer |
| Obstruction |
| Leakage (perforation) |
| Iron deficiency |
| Toxic megacolon |
| Inanition (wasting) |
| Strictures |

IBS Mimickers
• Enteric infections e.g. Giardia
• Lactose intolerance/other disaccharidase deficiency
• Crohn’s disease
• Celiac sprue
• Drug-induced diarrhea
• Diet-induced (excess tea, coffee, colas)
Treatment
- reassurance, explanation, support, aim for realistic goals
- relaxation therapy, biofeedback, hypnosis, stress reduction
- no therapeutic agent consistently effective, pain most difficult to control
- symptom-guided treatment
  - pain predominant
    - antispasmodic medication before meals (e.g. hyoscine, pinaverium, trimebutine)
    - increase dietary fibre (bran or psyllium)
  - tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRI)
  - IBS with diarrhea (IBS-D)
    - increase dietary fibre (bran or psyllium) to increase stool consistency
    - loperamide (Imodium®)
    - diphenoxylate (Lomotil®)
    - cholestyramine 4 g QID
  - IBS with constipation (IBS-C)
    - exercise and increase fibre in diet
    - osmotic or other laxatives
  - mixed (alternating constipation and diarrhea) (IBS-M)

Prognosis
- 80% improve over time
- most have intermittent episodes
- normal life expectancy

Constipation

Definition
- passage of infrequent or hard stools with straining (stool water <50 mL/d); bowel frequency <3 times/wk

Epidemiology
- increasing prevalence with age; F>M
- rare in Africa and India where stool weight is 3-4x greater than in Western countries

Etiology
- most common: idiopathic attributed to colon dysmotility but this is difficult to measure
- organic causes
  - medication side effects (narcotics, antidepressants) are the most common
  - intestinal obstruction, left sided colon cancer (consider in older patients), and fecal impaction
  - metabolic
    - DM
    - hypothyroidism
    - hypercalcemia, hypokalemia, uremia
  - neurological
    - intestinal pseudo-obstruction
    - Parkinson's disease
    - MS
  - collagen vascular disease (e.g. scleroderma)
  - painful anal conditions (e.g. fissures)

Clinical Presentation
- overlaps with IBS
- stool firm, difficult to expel, passed with straining, abdominal pain relieved by defecation, flatulence, overflow diarrhea, tenesmus, abdominal distension, infrequent BMs (<3/wk)

Investigations
- underlying disease rarely found if constipation is the only presenting symptom
  - only test indicated in this situation is a CBC (2013 recommendation of American Gastroenterology Association), but also consider TSH, calcium, and glucose
  - colon visualization if concomitant symptoms such as rectal bleeding, weight loss, or anemia (colonoscopy, CT colonography)
  - if refractory to treatment, consider classification based on colon transit time; can measure colonic transit time with radio-opaque markers that are ingested and followed with a series of plain film abdominal x-rays (normal: 70 h)
  1. normal = misperception of normal defecation (IBS)
  2. prolonged throughout = "colonic inertia" (infrequent bowel movements with gas/bloating, tends to occur in youth)
  3. outlet obstruction = inability to coordinate pelvic floor muscles to empty rectum, straining, stool in rectum on digital exam, tends to occur in old age
- combination of 1 and 3 common

Rifaximin Therapy for Patients with Irritable Bowel Syndrome Without Constipation

Purpose: Previous evidence suggests that gut flora may play an important role in the pathophysiology of IBS. This study evaluated rifaximin, a minimally absorbed antibiotic, in treating IBS without constipation.

Methods: Two phase 3, double-blind, placebo-controlled trials (TARGET 1 and TARGET 2). 1,260 patients who had IBS without constipation were randomly assigned to rifaximin (550 mg dose) or placebo, 3 times daily for 2 wk, with a follow-up of 10 wk. The primary endpoint was adequate self-reported relief of global IBS symptoms.

Results: Significantly more patients in the rifaximin group had adequate self-reported relief of global IBS symptoms compared to the placebo group during the first 4 wk after treatment (40.8% vs. 31.2% respectively). Also, more patients in the rifaximin group had adequate relief of bloating compared to the placebo group (39.5% vs. 28.7% respectively).

Conclusions: Rifaximin therapy for 2 wk provided significant relief of symptoms, bloating, abdominal pain, and stool consistency associated with IBS without constipation.
Treatment (In order of Increasing Potency)
- dietary fibre
  - useful if mild or moderate constipation, but not if severe
  - aim for 30 g daily, increase dose slowly
- surface-acting (soften and lubricate)
- docusate salts, mineral oils
- osmotic agents (effective in 2-3 d)
  - lactulose, sorbitol, magnesium salts (e.g. magnesium hydroxide, i.e. milk of magnesia)
  - lactitol, polyethylene glycol 3350
- cathartics/stimulants (effective in 24 h)
  - castor oil, senna (avoid prolonged use to prevent melanosis coli), bisacodyl
- enemas and suppositories (e.g. saline enema, phosphate enema, glycerin suppository, bisacodyl suppository)
- prokinetic agents (prucalopride)
- linacotide (increases water secretion of bowel)

Upper Gastrointestinal Bleeding

Definition
- bleeding proximal to the ligament of Treitz, see Gastrointestinal Tract, G2 (75% of GI bleeds)
- ligament of Treitz: suspensory ligament where fourth portion of the duodenum transitions to jejunum

Etiology
- above the GE junction
  - epistaxis
  - esophageal varices (10-30%)
  - esophagitis
  - esophageal cancer
  - Mallory-Weiss tear (10%)
- stomach
  - gastric ulcer (20%) (see Peptic Ulcer Disease, G12)
  - gastritis (e.g. from alcohol or post-surgery) (20%)
  - gastric cancer
  - gastric antral vascular ectasia (rare, associated with cirrhosis and CTD)
  - Dieulafoy’s lesion (very rare)
- duodenum
  - ulcer in bulb (25%)
  - aortoenteric fistula: usually only if previous aortic graft (see sidebar, G25)
- coagulopathy (drugs, renal disease, liver disease)
- vascular malformation (Dieulafoy’s lesion, AVM)

Clinical Features
- in order of decreasing severity of the bleed: hematochezia > hematemesis > coffee ground emesis > melena > occult blood in stool

Treatment (initial)
- stabilize patient (1-2 large bore IVs, IV fluids, monitor)
- send blood for CBC, cross and type, platelets, PT, PTT, electrolytes, BUN, Cr, LFTs
- keep NPO
- consider NG tube to determine upper vs. lower GI bleeding in some cases
- endoscopy (OGD): establish bleeding site + treat lesion
  - if bleeding peptic ulcer: most commonly used method of controlling bleeding is injection of epinephrine around bleeding point + thermal hemostasis (bipolar electrocoagulation or heater probe); less often thermal hemostasis may be used alone, but injection alone not recommended
  - endoclip
  - hemospray
- IV PPI: decrease risk of rebleed if endoscopic predictors of rebleeding seen (see prognosis section)
  - given to stabilize clot, not to accelerate ulcer healing
  - if given before endoscopy, decreases need for endoscopic therapeutic intervention
- for variceal bleeds, octreotide 50 µg loading dose followed by constant infusion of 50 µg/h
- consider IV erythromycin (or metoclopamid) to accelerate gastric emptying prior to gastroscopy to remove clots from stomach

Prognosis
- 80% stop spontaneously
- peptic ulcer bleeding: low mortality (2%) unless rebleeding occurs (25% of patients, 10% mortality)
- endoscopic predictors of rebleeding: spurt or ooze, visible vessel, fibrin clot
- can send home if clinically stable, bleed is minor, no comorbidities, endoscopy shows clean ulcer with no predictors of rebleeding
- H₂-antagonists have little impact on rebleeding rates and need for surgery
- esophageal varices have a high rebleeding rate (55%) and mortality (29%)
Approach to Iron Deficiency Anemia

Figure 8. Approach to iron deficiency anemia

Esophageal Varices

Etiology
- almost always due to portal HTN
- often accompanied by varices in stomach

Clinical Features
- characteristically massive upper GI bleeding

Prognosis
- risk of bleeding: 30% in 1st yr
- risk of rebleeding: 50-70% (20% mortality at 6 wk)

Investigations
- endoscopy

Management

Mallory-Weiss Tear

Definition
- longitudinal laceration in gastric mucosa on lesser curvature near GE junction (20% straddle junction, 5% in distal esophagus)

Etiology
- due to rapid increases in gastric pressure from retching/vomiting against a closed glottis
- hiatus hernia usually present
**Clinical Features**
- hematemesis ± melena, classically following an episode of retching without blood
- can lead to fatal hematemesis

**Management**
- 90% stop spontaneously
- if persistent: endoscopy with epinephrine injection ± clips or surgical repair

## Lower Gastrointestinal Bleeding

### Definition
- bleed distal to ligament of Treitz

### Etiology
- if blood per rectum with hemodynamic instability, rule out upper GI source
- diverticular (60% from right colon)
- vascular
  - angiodysplasia (small vascular malformations of the gut)
  - anorectal (hemorrhoids, fissures)
- neoplasm
  - cancer
  - polyps
- inflammation
  - colitis (ulcerative, infectious, radiation, ischemic)
- post-polypectomy

### Clinical Features
- hematochezia (see Figure 10)
- anemia
- occult blood in stool
- rarely melena

### Treatment
- treat underlying cause

![Figure 10. Approach to hematochezia](image)

**Colorectal Carcinoma**
- see General Surgery, GS35

**Colorectal Polyps**
- see General Surgery, GS34
**Familial Colon Cancer Syndromes**

- see General Surgery, GS34

**Benign Anorectal Disease**

- see General Surgery, GS39

---

**Liver**

### Investigations of Hepatobiliary Disease

#### A. TESTS OF LIVER FUNCTION

**Table 14. Tests of Liver Function**

<table>
<thead>
<tr>
<th>Test</th>
<th>What Do Levels Correlate With?</th>
<th>Increased by</th>
<th>How to Interpret</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prothrombin Time (PT or INR)</td>
<td>Hepatic protein synthesis All coagulation factors except VIII</td>
<td>Hepatocellular dysfunction Vitamin K deficiency (due to malnutrition, malabsorption, etc.)</td>
<td>PT/INR will promptly correct if vitamin K is administered, so increased PT/INR in absence of vitamin K deficiency is a reliable marker of hepatocellular dysfunction</td>
</tr>
<tr>
<td>Serum Albumin</td>
<td>Hepatic protein synthesis (and other causes listed in next column)</td>
<td>Hepatocellular dysfunction Malnutrition Renal or GI losses Significant inflammation Malignancy</td>
<td>Rule out potential causes other than hepatocellular dysfunction</td>
</tr>
<tr>
<td>Serum Direct Bilirubin*</td>
<td>Hepatic excretion from hepatocyte to biliary system</td>
<td>Liver dysfunction</td>
<td>Conjugation is preserved even in end stage liver failure, thus increased direct bilirubin indicates liver dysfunction</td>
</tr>
</tbody>
</table>

*Serum Bilirubin

- canalculus breakdown product of hemoglobin; metabolized in the reticuloendothelial system of liver, transported through biliary system, excreted via gut
- direct bilirubin = conjugated; indirect = unconjugated bilirubin

#### B. TESTS OF LIVER INJURY

- disproportionately increased AST or ALT = hepatocellular damage
  - ALT more specific to liver; AST from multiple sources (especially muscle)
  - elevation of both highly suggestive of liver injury
  - most common cause of elevated ALT is fatty liver
- disproportionately increased ALP (and GGT) = cholestasis (stasis of bile flow)
  - if ALP is elevated alone, rule out bone disease by fractionating ALP and/or checking GGT
  - if ALP elevation out of proportion to ALT/AST elevation, consider
    1. obstruction of common bile duct (extraluminal = pancreatic Ca, lymphoma; intraluminal = stones, cholangiocarcinoma, sclerosing cholangitis, helminths)
    2. destruction of microscopic ducts (e.g. PBC)
    3. bile acid transporter defects (drugs, intrahepatic cholestasis of pregnancy)
    4. infiltration of the liver (liver metastases, lymphoma, granulomas, amyloid)

---

**Acute Viral Hepatitis (General)**

**Definition**

- viral hepatitis lasting <6 mo

**Clinical Features**

- most are subclinical
- flu-like prodrome may precede jaundice by 1-2 wk
  - N/V, anorexia, taste/smell disturbance, headaches, fatigue, myalgia, low-grade fever
  - arthralgia and urticaria (especially HBV)
- only some progress to icteric (clinical jaundice) phase, lasting days to weeks
  - pale stools and dark urine 1-5 d prior to icteric phase
  - hepatomegaly and RUQ pain
  - splenomegaly and cervical lymphadenopathy (10-20% of cases)

---

All clotting factors except factor VIII and von Willebrand factor are exclusively synthesized in the liver. Factor VIII is also produced in the endothelium.

ALT > AST = most causes of hepatitis

AST > ALT = alcoholic liver disease or other causes of hepatitis (i.e. non-alcoholic liver disease) that have progressed to advanced cirrhosis.

Serum Transaminases >1000 due to

- Viral hepatitis
- Drugs
- Autoimmune hepatitis
- Hepatic ischemia
- Less often, common bile duct stone
Investigations
- AST and ALT (>10-20x normal in hepatocellular necrosis)
- ALP minimally elevated
- viral serology, particularly the IgM antibody directed to the virus

Treatment
- supportive (hydration, diet)
- usually resolves spontaneously, but if severe HBV infection, treatment with entecavir should be considered; in anicteric hepatitis C, anti-viral treatment should be considered (see hepatitis C)
- indications for hospitalization: encephalopathy, coagulopathy, severe vomiting, hypoglycemia

Prognosis
- poor prognostic indicators: comorbidities, persistently high bilirubin (>340 mmol; 20 mg/dL), increased INR, decreased albumin, hypoglycemia

Complications
- cholestasis (most commonly associated with HAV infection)
- hepatocellular necrosis: AST, ALT >10-20x normal, ALP and bilirubin minimally increased, increased cholestasis

Hepatitis A Virus
- RNA virus
- fecal-oral transmission; incubation period 4-6 wk
- diagnosed by elevated transaminases, positive anti-HAV IgM
- in children: characteristically asymptomatic
- in adults: fatigue, nausea, arthralgia, fever, jaundice
- can cause acute liver failure and subsequent death (<1-5%)
- can relapse, but never becomes chronic

Hepatitis B Virus

<table>
<thead>
<tr>
<th>Table 15. Hepatitis B Serology</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
</tr>
<tr>
<td>Acute HBV</td>
</tr>
<tr>
<td>Chronic (e-Ag positive) HBV (generally high HBV DNA)</td>
</tr>
<tr>
<td>Chronic (e-Ag negative) HBV (generally low HBV DNA)</td>
</tr>
<tr>
<td>Resolved infection</td>
</tr>
<tr>
<td>Immunization</td>
</tr>
</tbody>
</table>

Figure 11. Time course of acute hepatitis B infection

Epidemiology
- 4 phases of chronic hepatitis B: not all carriers will go through all 4 phases, but all carriers will have positive HBsAg
  1. immune tolerance: extremely high HBV-DNA (>20,000 IU/mL), HBeAg positive, but normal ALT/AST; due to little immune control and minimal immune-mediated liver damage; characteristic of perinatal infection (or ‘incubation period’ in adult with newly-acquired HBV)
2. immune clearance (or immunoactive): falling but still elevated HBV-DNA levels (>20,000 IU/mL), HBeAg positive; due to immune attack on the virus and immune-mediated liver damage; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

3. immune control: lower HBV-DNA (<20,000 IU/mL), HBeAg negative, anti-HBe positive, ALT/AST normal; due to immune control without immune-mediated liver damage; risk of reactivation to phase 2 (clinically resembles acute hepatitis B), especially with immunosuppression e.g. corticosteroids or chemotherapy

4. immune escape ("core or precore mutant"): elevated HBV-DNA (>2,000 IU/mL), HBeAg negative because of pre-core or core promoter gene mutation, anti-HBe positive, ALT/AST high; characterized by progressive disease without treatment and increasing liver fibrosis (sometimes progressing to cirrhosis and/or hepatocellular carcinoma); likely to benefit from treatment

Treatment
- counselling: 40% of men and 10% of women with perinatal infection will die from HBV-related complications
- prolonged immune-mediated damage leads to higher risk of liver fibrosis
- hepatocellular carcinoma screening with ultrasound q6mo, especially if high serum HBV-DNA levels, cirrhosis, men, (age >40 in Asian men, >50 in Asian women, and >20 in African descent)
- consider pharmacological therapy if
  - 1. HBeAg positive + HBV-DNA >20, 000 IU/mL + elevated ALT; or
  - 2. HBeAg negative + HBV-DNA >2,000 IU/mL + elevated ALT ± stage ≥2 fibrosis on liver biopsy
- 3. treat to reduce serum HBV-DNA to undetectable level
- treatment options: interferon, tenofovir, entacavir, lamivudine
- vaccinate against HAV if serology negative (to prevent further liver damage)
- follow blood and sexual precautions

Hepatitis D
- defective RNA virus requiring HBsAg for entry into hepatocyte, therefore infects only patients with HBV; causes more aggressive disease than hepatitis B virus alone
- coinfection: acquire HDV and HBV at the same time
- better prognosis than superinfection (acute HDV infection on pre-existing HBV infection)
- HDV can present as ALF and/or accelerate progression to cirrhosis
- treatment: low-dose interferon (20% response) and liver transplant for end-stage disease

Hepatitis C Virus
- RNA virus (7 genotypes; genotype 1 is most common in North America)
- blood-borne transmission; sexual transmission is "inefficient"
- major risk factor: injection drug use
- other risk factors: blood transfusion received before 1992 (or received in developing world), tattoos, intranasal cocaine use
- clinical manifestation develops 6-8 wk after exposure
  - symptoms mild and vague (fatigue, malaise, nausea) therefore not commonly diagnosed in acute stage

Diagnosis
- suspected on basis of elevated ALT/AST and positive serum anti-HCV
- diagnosis established by detectable HCV-RNA in serum
- virus genotype correlates with response to treatment but not prognosis
  - serum HCV-RNA inversely correlates with response to treatment
- normal transaminases can have underlying cirrhosis on biopsy, but otherwise excellent prognosis

Treatment
- blood-borne precautions; vaccinate for hepatitis A and B if serology negative; avoid alcohol
- clearest indication for treatment is in subgroup likely to develop clinically significant liver disease
  - persistently elevated transaminases, liver biopsy shows fibrosis/cirrhosis and at least moderately severe necrosis/inflammation
- previous standard of care was pegylated interferon-α + ribavirin + a direct-acting anti-viral agent aiming to clear HCV infection, but <90% success rate and side effects common
- as of 2015, all oral interferon-free regimens (e.g. sofosbuvir/ledipasvir or ombitasvir/paritaprevir/ritonavir+dasabuvir) are now becoming the standard of care with >90% success rate including those who failed previous interferon-based treatment
Prognosis
- 80% of acute hepatitis C become chronic (of these 20% evolve to cirrhosis)
- risk of hepatocellular carcinoma increases if cirrhotic
- can cause cryoglobulinemia; associated with membranoproliferative glomerulonephritis, lymphoma

Table 16. Characteristics of the Viral Hepatitides

<table>
<thead>
<tr>
<th></th>
<th>HAV</th>
<th>HBV</th>
<th>HCV</th>
<th>HDV</th>
<th>HEV</th>
<th>CMV</th>
<th>EBV</th>
<th>Yellow Fever</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virus Family</td>
<td>Picornaviridae</td>
<td>Hepadnaviridae</td>
<td>Flaviviridae</td>
<td>Deltaviridae</td>
<td>Caliciviridae</td>
<td>Herpesviridae</td>
<td>Herpesviridae</td>
<td>Flavivirus</td>
</tr>
<tr>
<td>Genome</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
<td>RNA</td>
<td>DNA</td>
<td>RNA</td>
<td>RNA</td>
</tr>
<tr>
<td>Envelope</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Transmission</td>
<td>Fecal-oral</td>
<td>Parenteral/sexual or equivalent</td>
<td>Vertical</td>
<td>Parenteral (transfusion, IVDU, sexual [&lt;HBV])</td>
<td>Non-parenteral (close contact in endemic areas)</td>
<td>Parenteral (blood products, IVDU); sexual transmission is inefficient</td>
<td>Fecal-oral (endemic: Africa, Asia, central America, India, Pakistan)</td>
<td>Close contacts, most body fluids</td>
</tr>
<tr>
<td>Incubation</td>
<td>4-6 wk</td>
<td>6 wk-6 mo</td>
<td>2-26 wk</td>
<td>3-13 wk</td>
<td>2-8 wk</td>
<td>20-60 d</td>
<td>30-50 d</td>
<td>3-6 d</td>
</tr>
<tr>
<td>Onset</td>
<td>Usually abruptly</td>
<td>Usually insidious</td>
<td>Insidious</td>
<td>Usually abruptly</td>
<td>Usually abrupt</td>
<td>Variable</td>
<td>Variable</td>
<td>Usually abrupt</td>
</tr>
<tr>
<td>Communicability</td>
<td>2-3 wk in late incubation to early clinical phase</td>
<td>Acute hepatitis in most adults, 10% of children</td>
<td>HBSAg+ state highly communicable increased during third trimester or early post-partum</td>
<td>Communicable prior to overt symptoms and throughout chronic illness</td>
<td>Infectious only in presence of HBV (HBSAg required for replication)</td>
<td>Unknown</td>
<td>Variable – dormant or persistent</td>
<td>Communicable highest during year after primary infection but never zero</td>
</tr>
<tr>
<td>Chronicity</td>
<td>None, although can relapse</td>
<td>5% adults, 90% infants</td>
<td>80%, 20% of which develop cirrhosis</td>
<td>5%</td>
<td>None</td>
<td>Common; latent</td>
<td>Common; latent</td>
<td>Infection confers lifelong immunity</td>
</tr>
<tr>
<td>Serology</td>
<td>Anti-HAV (IgM)</td>
<td>See Table 15</td>
<td>HCV-RNA Anti-HCV (IgG/IgM)</td>
<td>HBSAg Anti-HDV (IgG/IgM)</td>
<td>Anti-HEV (IgG/IgM)</td>
<td>Anti-CMV (IgM/IgG)</td>
<td>Monospot; anti-EBV IgM/IgG, EBV DNA quantitation</td>
<td>Anti-YF (IgM/IgG)</td>
</tr>
<tr>
<td>Immunity</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Yes</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>Yes</td>
</tr>
<tr>
<td>Vaccine</td>
<td>Havrix, 2 doses q6mo, combined with Twinrix at 0, 7, and 21 d</td>
<td>Recombivax HBTM, age 11-15, 2 doses q6mo</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>YF-VAX, 1 dose booster q10yr</td>
</tr>
<tr>
<td>Management</td>
<td>General hygiene</td>
<td>Treat close contacts (anti-HAV Ig)</td>
<td>Prophylaxis for high-risk groups (HAV vaccine ± HAV Ig) unless immune</td>
<td>Prevention: HBV vaccine and/or hepatitis B Ig (HBIG) for needlestick, sexual contact, infants of infected mothers unless already immune Rx: oral antivirals vs interferon if indications met</td>
<td>Prevention: no vaccine Rx: IFN – ribavirin ± protease inhibitor; although all oral anti-viral (IFN-free) therapy now available is highly efficacious</td>
<td>Prevention: HBV vaccine</td>
<td>Prevention: general hygiene, no vaccine</td>
<td>In high risk transplant patients: CMV Ig and anti-virals (ganciclovir, valganciclovir)</td>
</tr>
<tr>
<td>Acute Mortality</td>
<td>0.1-0.3%</td>
<td>0.5-2%</td>
<td>1%</td>
<td>2-20% coinfection with HBV, 30% superinfection</td>
<td>Preiscopes HBV carriers to more severe hepatitis and faster progression to cirrhosis</td>
<td>1-2% overall, 10-20% in pregnancy</td>
<td>Rare in immunocompetent adults</td>
<td>Rare</td>
</tr>
<tr>
<td>Oncogenicity</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Complications</td>
<td>Hepatocellular carcinoma secondary to cirrhosis, serum sickness-like syndrome, glomerulonephritis, cryoglobulinemia, polyarteritis nodosa, porphyria cutanea tarda</td>
<td>Hepatocellular carcinoma in 2-5% of cirrhosis per yr, cryoglobulinemia, B-cell non-Hodgkin lymphoma</td>
<td>Leukocytoclastic vasculitis, membranous glomerulonephropathy</td>
<td>Mild, except in third trimester (10-20% fulminant liver failure)</td>
<td>5% of newborns with multiple handicaps</td>
<td>Immunocompromised patients at risk of CMV-induced hepatitis, retinitis, colitis, esophagitis, pneumonitis</td>
<td>Associated with Burkitt’s lymphoma and nasopharyngeal carcinoma (rare in Western world)</td>
<td>Can cause a recurrent toxic phase with liver damage, GI bleeding, and high mortality rates</td>
</tr>
</tbody>
</table>
Autoimmune Chronic Active Hepatitis

- diagnosis of exclusion: rule out viruses, drugs, metabolic, or genetic causes
- can be severe: 40% mortality at 6 mo without treatment
- extrahepatic manifestations
  - sicca, Raynaud's, thyroiditis, Sjögren's, arthralgias
  - hypergammaglobulinemia
  - anti-smooth muscle antibody elevation is most characteristic; also elevations in
    - anti-LKM elevation (liver kidney microsome), especially in children
    - less specific: elevated ANA, RF
  - can have false positive viral serology (especially anti-HCV)
  - biopsy – periportal (zone 1) and interface inflammation and necrosis
- treatment: corticosteroids (80% respond) ± azathioprine (without this, most will relapse as corticosteroids are withdrawn)

Drug-Induced Liver Disease

Table 17. Classification of Hepatotoxins

<table>
<thead>
<tr>
<th>Example</th>
<th>Direct</th>
<th>Indirect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen, CCl₄</td>
<td>Phenytoin, INH</td>
<td></td>
</tr>
<tr>
<td>Dose-Dependence</td>
<td>Usual</td>
<td>Unusual</td>
</tr>
<tr>
<td>Latent Period</td>
<td>Hours-days</td>
<td>Weeks-months</td>
</tr>
<tr>
<td>Host Factors</td>
<td>Not important</td>
<td>Very important</td>
</tr>
<tr>
<td>Predictable</td>
<td>Yes</td>
<td>No (idiosyncratic)</td>
</tr>
</tbody>
</table>

Specific Drugs

- acetaminophen
  - metabolized by hepatic cytochrome P450 system
  - can cause ALF (transaminases >1,000 U/L followed by jaundice and encephalopathy)
  - requires 10-15 g in healthy, 4-6 g in alcoholics/anticonvulsant users
  - mechanism: high acetaminophen dose saturates glucuronidation and sulfation elimination pathways → reactive metabolite is formed → covalently binds to hepatocyte membrane
  - presentation
    - first 24 h: N/V (usually within 4-12 h of overdose)
    - 24-48 h: asymptomatic, but ongoing hepatic necrosis resulting in increased transaminases
    - >48 h: continued hepatic necrosis possibly complicated with ALF or resolution
  - note: potential delay in presentation in sustained-release products
  - blood levels of acetaminophen correlate with the severity of hepatic injury, particularly if time of ingestion known
  - therapy
    - gastric lavage/emacsion (if <2 h after ingestion)
    - oral activated charcoal
    - N-acetylcysteine (NAC, Mucomyst®) can be given PO or IV (most effective within 8-10 h of ingestion, but should be given no matter when time of ingestion)
      - promotes hepatic glutathione regeneration
      - no recorded fatal outcomes if NAC given before increase in transaminases
- chlorpromazine: cholestasis in 1% after 4 wk; often with fever, rash, jaundice, pruritus, and eosinophilia
- INH (isoniazid)
  - 20% develop elevated transaminases but <1% develop clinically significant disease
  - susceptibility to injury increases with age
- methotrexate
  - causes fibrosis/cirrhosis; increased risk in the presence of obesity, DM, alcoholism (i.e. with underlying risk for pre-existing fatty liver)
  - scarring develops without symptoms or changes in liver enzymes, therefore biopsy may be needed in long-term treatment
- amiodarone: can cause same histology and clinical outcome as alcoholic hepatitis
- others: azoles, statins, methylxop, phenytoin, propylthiouracil (PTU), rifampin, sulfonamides, tetracyclines
- herbs: chaparral, Chinese herbs (e.g. germander, comfrey, bush tea)

Hy's Law: drug-induced hepatocellular jaundice indicates a mortality of at least 10%
Wilson’s Disease

Definition
• autosomal recessive defect in copper metabolism (gene ATP7B)

Etiology
• decreased biliary excretion of copper plus decreased incorporation of copper into ceruloplasmin

Clinical Features
• liver: acute hepatitis, acute liver failure, chronic active hepatitis, cirrhosis, low risk of hepatocellular carcinoma
• eyes: Kayser-Fleischer rings (copper deposits in Descemet’s membrane); more common in patients with CNS involvement, present in 50% if only liver involvement
• CNS: basal ganglia (wing flapping tremor, Parkinsonism), cerebellum (dysarthria, dysphagia, incoordination, ataxia), cerebrum (psychosis, affective disorder)
• kidneys: Fanconi’s syndrome (proximal tubule transport defects) and stones
• blood: intravascular hemolysis; may be initial presentation in fulminant hepatitis
• joints: arthritis, bone demineralization, calcifications

Investigations
• suspect if increased liver enzymes with clinical manifestations at young age (<30); especially combination of liver disease with dystonia, psychiatric symptoms
• screening tests
  1. reduced serum ceruloplasmin (<50% of normal)
  2. Kayser-Fleischer rings (usually require slit-lamp examination)
  3. increased urinary copper excretion
• gold standard
  1. increased copper on liver biopsy by quantitative assay
  2. genetic analysis imperfect as many mutations in ATP7B are possible

Treatment
• 4 drugs available
  1. penicillamine chelates copper, poorly tolerated
  2. trientine chelates copper
  3. zinc impairs copper excretion in stool and decreases copper absorption from gut
  4. tetrathiomolybdate preferred if neurological involvement
• screen relatives
• liver transplant in severe cases

Hemochromatosis

Definition
• excessive iron storage causing multiorgan system dysfunction (liver, in particular) with total body stores of iron increased to 20–40 g (normal 1 g)

Etiology
• primary (hereditary) hemochromatosis
  ▪ hepcidin deficiency results in ongoing gut absorption of iron despite adequate iron stores
  ▪ results in ongoing gut absorption of iron despite adequate iron stores
• secondary hemochromatosis
  ▪ parenteral iron overload (e.g. transfusions)
  ▪ chronic hemolytic anemia: thalassemia, pyruvate kinase deficiency
  ▪ excessive iron intake

Epidemiology
• hereditary hemochromatosis most common in Northern European descent
  ▪ primarily due to common recessive gene (HFE, 5%); 1/400 patients are homozygotes

Clinical Features
• usually presents with trivial elevation in serum transaminases
• liver: cirrhosis (30%), HCC (200x increased risk) – most common cause of death (1/3 of patients)
• pancreas: DM, chronic pancreatitis
• skin: bronze or grey (due to melanin, not iron)
• heart: dilated cardiomyopathy
• pituitary: hypogonadotropic hypogonadism (impotence, decreased libido, amenorrhea)
• joints: arthralgia (any joint, but especially MCP joints), chondrocalcinosis
Investigations
- screening for individuals with clinical features and/or family history (1/4 chance of sibling having the disease)
  - transferrin saturation (free Fe²⁺/TIBC) >45%
  - serum ferritin >400 ng/mL
  - HFE gene analysis: 90% of primary hemochromatosis involves C282Y allele, while H63D and S65C alleles also commonly involved and screened
- liver biopsy (generally used to detect cirrhosis or if potential for other causes of liver disease)
  - markers of advanced fibrosis: if any of the following are present at the time of diagnosis → age >40, elevated liver enzymes, or ferritin >1000
  - considered if compound heterozygote and potential other cause of liver injury (e.g. fatty liver, etc.)
  - if C282Y/C282Y and no markers of advanced fibrosis, then biopsy generally not needed
- HCC screening if cirrhosis

Treatment
- phlebotomy: weekly or q2wk then lifelong maintenance phlebotomies q2-6mo
- deferoxamine if phlebotomy contraindicated (e.g. cardiomyopathy, anemia)
- primary hemochromatosis responds well to phlebotomy
- secondary hemochromatosis usually requires chelation therapy (administration of agents that bind and sequester iron, and then excreted)

Prognosis
- normal life expectancy if treated before the development of cirrhosis or DM

Alcoholic Liver Disease

Definition
- fatty liver (all alcoholics): always reversible if alcohol stopped
- alcoholic hepatitis (35% of alcoholics): usually reversible if alcohol stopped
- cirrhosis (10-15% of alcoholics): potentially irreversible

Pathophysiology
- several mechanisms, poorly understood
- ethanol oxidation to acetaldehyde
  - reduces NAD⁺ to NADH; increased NADH decreases ATP supply to liver, impairing lipolysis so fatty acids and triglycerides accumulate in liver
  - binds to hepatocytes evoking an immune reaction
- ethanol increases gut permeability leading to increased bacterial translocation
- alcohol metabolism causes
  - relative hypoxia in liver zone III (near central veins; poorly oxygenated) > zone I (around portal tracts, where oxygenated blood enters)
  - necrosis and hepatic vein sclerosis
- histology of alcoholic hepatitis
  - ballooned (swollen) hepatocytes often containing Mallory bodies, characteristically surrounded by neutrophils
  - large fat globules
  - fibrosis: space of Disse and perivenular

Clinical Features
- >2-3 standard drinks/d in females and >3-6 standard drinks/d in men for >10 yr leads to cirrhosis, but only in about 10-20% of those who consume this amount daily on a continuous basis; cirrhosis risk increases with amount of alcohol consumed above threshold
- clinical findings do not accurately predict type of liver involvement
  - fatty liver
    - mildly tender hepatomegaly; jaundice rare
    - mildly increased transaminases <5x normal
  - alcoholic hepatitis
    - variable severity: mild to fatal liver failure
    - mild: stops drinking because feels unwell, resumes when feeling better (if assessed, findings of hepatitis, potentially mild jaundice, and mildly elevated INR)
    - severe: stops drinking but feels unwell, low grade fever, RUQ discomfort, increased white blood cell count – mimics RLL pneumonia and cholecystitis

Investigations
- blood tests are non-specific, but in general
  - AST:ALT ≥2:1 (usually <300)
  - increased GGT
  - CBC: increased MCV, increased WBC
Treatment
• alcohol cessation (see Psychiatry, PS25)
  ▪ Alcoholics Anonymous, disulfiram, naltrexone, acamprosate
• multivitamin supplements (especially thiamine)
• caution with drugs metabolized by the liver
• if icteric alcoholic hepatitis prednisone 40 mg OD x 28 d in subgroup with elevated bilirubin and INR (Maddrey’s discriminant function > 32); but contraindicated in GI bleeding, renal failure, infection, pancreatitis
  ▪ response (and subsequent decision to continue treatment) predicted by day 7 bilirubin (Lille score)
• pentoxyfilline reported to be beneficial in one of three studies, but most definitive trial shows no benefit (see Landmark Trials, G51)

Prognosis
• Maddrey’s discriminant function (based on PT and bilirubin) and MELD predict mortality and guide treatment
• fatty liver: complete resolution with cessation of alcohol intake
• alcoholic hepatitis mortality
  ▪ immediate: 30%-60% in the first 6 mo if severe
  ▪ with continued alcohol: 70% in 5 yr
  ▪ with cessation: 30% in 5 yr

Non-Alcoholic Fatty Liver Disease

Definition
• spectrum of disorders characterized by macrovesicular hepatic steatosis
• most common cause of liver disease in North America

Etiology
• pathogenesis not well elucidated; insulin resistance implicated as key mechanism, leading to hepatic steatosis
• changes indistinguishable from those of alcoholic hepatitis despite negligible history of alcohol consumption

Risk Factors
• likely a component of the metabolic syndrome along with type 2 DM, HTN, hypertriglyceridemia
• rapid weight loss or weight gain

Clinical Features
• often asymptomatic
• may present with fatigue, malaise, and vague RUQ discomfort
• elevated serum triglyceride/cholesterol levels and insulin resistance

Investigations
• elevated serum AST, ALT ± ALP; AST/ALT <1
• presents as echogenic liver texture on ultrasound
• liver biopsy diagnostic, but often necessary only for prognosis

Treatment
• no proven effective therapy other than gradual weight loss
• some evidence for vitamin E (800 U daily) in select groups
  ▪ pioglitazone can be considered if DM concomitantly present, but results in weight gain
• modification of risk factors is generally recommended, especially gradual weight reduction
• optimization of therapy for DM, hyperlipidemia, HTN
• some evidence for benefits of coffee drinking (3 cups per day)

Prognosis
• most die from cardiovascular or cerebrovascular disease
• better prognosis than alcoholic hepatitis
  ▪ <25% progress to cirrhosis over a 7-10 yr period
• risk of progression increases if inflammation or scarring occurs alongside fat infiltration (non-alcoholic steatohepatitis)
• other clinical indicators of unfavourable prognosis: DM, age, metabolic syndrome
Acute Liver Failure (formerly Fulminant Hepatic Failure)

**Definition**
- severe decline in liver function characterized by coagulation abnormality (INR>1.5) and encephalopathy
- in setting of previously normal liver
- rapid (<26 wk duration)

**Etiology**
- drugs (especially acetaminophen), hepatitis B (measure anti-HBc, IgM fraction because sometimes HBV-DNA and even HBsAg rapidly becomes negative), hepatitis A, hepatitis C (rare), ischemic, idiopathic

**Treatment**
- correct hypoglycemia, monitor level of consciousness, prevent GI bleeding with PPI, monitor for infection and multiorgan failure (usually requires ICU)
- consider liver biopsy before INR becomes too high
- chief value is to exclude chronic disease, less helpful for prognosis
- liver transplant (King's College criteria can be used as prognostic indicator): consider early, especially if time from jaundice to encephalopathy >7 d (e.g. not extremely rapid), age <10 or >40, cause is drug or unknown, bilirubin >300 µmol/L, INR >3.5, creatinine >200 µmol/L

Cirrhosis

**Definition**
- liver damage characterized by diffuse distortion of the basic architecture and replacement with scar tissue and formation of regenerative nodules
- Stage 1 cirrhosis is compensated and asymptomatic, can last for 10-20 yr with almost normal life expectancy
- Stage 2 cirrhosis is the onset of first decompensation, typically development of ascites (most common), variceal bleeding, encephalopathy

**Etiology**
- fatty liver (alcoholic or non-alcoholic fatty liver disease)
- chronic viral hepatitis (B, B+D, C; not A or E)
- autoimmune hepatitis
- hemochromatosis
- primary biliary cirrhosis
- chronic hepatic congestion
  - cardiac cirrhosis (chronic right heart failure, constrictive pericarditis)
  - hepatic vein thrombosis (Budd-Chiari)
- cryptogenic (i.e. no identifiable cause, although many of these patients may represent "burnt-out NASH")
  - rare: Wilson's disease, Gaucher's disease, α1-antitrypsin deficiency

**Investigations**
- definitive diagnosis is histologic (liver biopsy)
- other tests may be suggestive
  - blood work: fall in platelet count <150 is the earliest finding, followed many years later with rise in INR, fall in albumin, rise in bilirubin, fall in glucose level (pre-terminal event)
  - FibroTest: combination of various clinical and biochemical markers that can predict degree of fibrosis
  - imaging
    - U/S is the primary imaging modality but only finds advanced cirrhosis
    - CT to look for varices, nodular liver texture, splenomegaly, ascites
    - Ultrasound elastography (FibroScan): non-invasive tool using elastography (variable availability)
    - gastroscopy: varices or portal gastropathy

**Treatment**
- treat underlying disorder
- decrease insults (e.g. alcohol cessation, hepatotoxic drugs, immunize for Hep A and B if non-immune)
- follow patient for complications (esophageal varices, ascites, HCC defines stage 2 cirrhosis)
- prognosis: Child-Pugh Score and MELD score
- liver transplantation for end-stage disease if no alcohol for >6 mo; use MELD score

Figure 12. Progression of liver dysfunction based on liver function tests – the "W"

MELD (Model for End Stage Liver Disease)
- Predicts 3 mo survival and used to stratify patients on transplant list
- Based on creatinine, INR, and total bilirubin
Table 18. Child-Pugh Score and Interpretation

<table>
<thead>
<tr>
<th>Classification</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin (µmol/L)</td>
<td>&lt;34</td>
<td>34-51</td>
<td>&gt;51</td>
</tr>
<tr>
<td>Serum albumin (g/L)</td>
<td>&gt;35</td>
<td>28-35</td>
<td>&lt;28</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.7</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
</tr>
<tr>
<td>Presence of ascites</td>
<td>Absent</td>
<td>Controllable</td>
<td>Refractory</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>Absent</td>
<td>Minimal</td>
<td>Severe</td>
</tr>
</tbody>
</table>

Interpretation

<table>
<thead>
<tr>
<th>Points</th>
<th>Class</th>
<th>Life Expectancy</th>
<th>Perioperative Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td>A</td>
<td>15-50 yr</td>
<td>10%</td>
</tr>
<tr>
<td>7-9</td>
<td>B</td>
<td>Candidate for transplant</td>
<td>30%</td>
</tr>
<tr>
<td>10-15</td>
<td>C</td>
<td>1-3 mo</td>
<td>82%</td>
</tr>
</tbody>
</table>

Score: 5-6 (Child’s A), 7-9 (Child’s B), 10-15 (Child’s C)

*Note: Child’s classification is rarely used for shunting, (TIPS or other surgical shunts) but is still useful to quantitate the severity of cirrhosis

Complications

- hematologic changes in cirrhosis
  - pancytopenia from hypersplenism: platelets first, then WBC, then hemoglobin
  - decreased clotting factors resulting in elevated INR
  - relationship of INR to bleeding tendency is controversial; some patients may be hypocoagulable, others may be hypercoagulable
- variceal bleeds
  - half of patients with cirrhosis have gastroesophageal varices and one-third of these develop hemorrhage with an overall mortality of >30%
  - hepatic venous pressure gradient (HVPG) ≥10 mmHg is the strongest predictor of variceal development
  - treatment: resuscitation, antibiotic prophylaxis, vasoactive drugs (e.g. octreotide IV) combined with endoscopic band ligation or sclerotherapy, TIPS
- renal failure in cirrhosis
  - classifications
    - pre-renal (usually due to over-diuresis)
    - acute tubular necrosis
    - HRS
      - Type I: sudden and acute renal failure (rapid doubling of creatinine over 2 wk)
      - Type II: gradual increase in creatinine with worsening liver function (creatinine doubling over years)
  - HRS can occur at any time in severe liver disease, especially after
    - overdiuresis or dehydration, such as diarrhea, vomiting, etc.
    - GI bleed
    - sepsis
  - treatment for hepatorenal syndrome (generally unsuccessful at improving long-term survival)
    - for type I HRS: octreotide + midodrine + albumin (increases renal blood flow by increasing systemic vascular resistance)
    - definitive treatment is liver transplant
- hepatopulmonary syndrome
  - majority of cases due to cirrhosis, though can be due to other chronic liver diseases, such as non-cirrhotic portal HTN
  - thought to arise from ventilation-perfusion mismatch, intrapulmonary shunting and limitation of oxygen diffusion, failure of damaged liver to clear circulating pulmonary vasodilators vs. production of a vasodilating substance by the liver
  - clinical features
    - hyperdynamic circulation with cardiac output >7 L/min at rest and decreased pulmonary + systemic resistance (intrapulmonary shunting)
    - dyspnea, platypnea (increase in dyspnea in upright position, improved by recumbency), and orthodeoxia (desaturation in the upright position, improved by recumbency)
    - diagnosis via contrast-enhanced echocardiography: inject air bubbles into peripheral vein; air bubbles appear in left ventricle after third heartbeat (normal = no air bubbles; in ventricular septal defect, air bubbles seen <3 heart beats)
    - only proven treatment is liver transplantation

Usual causes of death in cirrhosis: renal failure (hepatorenal syndrome), sepsis, GI bleed, or HCC

Hepatorenal Syndrome vs. Pre-Renal Failure – Difficult to Differentiate
- Similar blood and urine findings, (see Nephrology, NP17)
- Urine sodium: very low in hepatorenal; low in pre-renal
- Intravenous fluid challenge: giving volume expanders improves pre-renal failure, but not hepatorenal syndrome

Hepatopulmonary Syndrome
- Clinical triad
  - Liver disease
  - Increased alveolar-arterial gradient while breathing room air
  - Evidence for intrapulmonary vascular abnormalities
- Fibrosis may regress and disappear if cause of liver injury is treated or resolves
**Hepatocellular Carcinoma**

- see General Surgery, GS45

**Liver Transplantation**

- see General Surgery, GS46

**Portal Hypertension**

Definition

- pressure gradient between hepatic vein pressure and wedged hepatic vein pressure (corrected sinusoidal pressure) >5 mmHg

Pathophysiology

- 3 sites of increased resistance (remember pressure = flow x resistance)
  - pre-sinusoidal (e.g. portal vein thrombosis, schistosomiasis, sarcoidosis)
  - sinusoidal (e.g. cirrhosis, alcoholic hepatitis)
  - post-sinusoidal (e.g. right-sided heart failure, hepatic vein thrombosis, veno-occlusive disease, constricive pericarditis)

Complications

- GI bleeding from varices in esophagus, less commonly in stomach, even less frequently from portal hypertensive gastropathy
- ascites
- hepatic encephalopathy
- thrombocytopenia
- renal dysfunction
- sepsis
- arterial hypoxemia

Treatment

- non-selective β-blockers (propanolol, nadolol) decrease risk of bleeding from varices
- TIPS: to decrease portal venous pressure
  - radiologically inserted shunt between portal and hepatic vein via transjugular vein catheterization and percutaneous puncture of portal vein
  - can be used to stop acute bleeding or prevent rebleeding or treat ascites
  - shunt usually remains open for <1 yr
  - complications: hepatic encephalopathy, deterioration of hepatic function
  - contraindicated with severe liver dysfunction
  - most commonly used as a “bridge” to liver transplant
- other surgically created shunts: portacaval, distal spleno-renal (Warren shunt) - all used only rarely in the modern era

**Hepatic Encephalopathy**

Definition

- spectrum of potentially reversible neuropsychiatric syndromes secondary to liver disease diagnosed after ruling out other causes for symptoms (e.g. structural/metabolic)

Pathophysiology

- portosystemic shunt around hepatocytes and decreased hepatocellular function increase level of systemic toxins (believed to be ammonia from gut, mercaptans, fatty acids, amino acids) which go to the brain
Precipitating Factors
- nitrogen load (GI bleed, protein load from food intake, renal failure, constipation)
- drugs (narcotics, CNS depressants)
- electrolyte disturbance (hypokalemia, alkalosis, hypoxia, hypovolemia)
- infection (spontaneous bacterial peritonitis)
- deterioration in hepatic function or superimposed liver disease

Stages
- I: apathy, restlessness, reversal of sleep-wake cycle, slowed intellect, impaired computational abilities, impaired handwriting
- II: asterixis, lethargy, drowsiness, disorientation
- III: stupor (rousable), hyperactive reflexes, extensor plantar response (upgoing Babinski)
- IV: coma (response to painful stimuli only)

Investigations
- clinical diagnosis: supported by laboratory findings and exclusion of other neuropsychiatric diseases
- rule out
  - non-liver-related neuropsychiatric disease in a patient with liver problems (e.g. alcohol withdrawal or intoxication, sedatives, subdural hematoma, metabolic encephalopathy)
  - causes of metabolic encephalopathy (e.g. renal failure, respiratory failure, severe hyponatremia, hypoglycemia)
- characteristic EEG findings: diffuse (non-focal), slow, high amplitude waves
- serum ammonia levels increased, but not often necessary to measure in routine clinical use

Treatment
- treat underlying precipitating factors
- decrease generation of nitrogenous compounds
  - routine protein restriction is no longer recommended given patients generally have concurrent malnutrition and muscle wasting; however, vegetable protein is better tolerated than animal protein
  - lactulose: titrated to achieve 2-3 soft stools/d
    - prevents diffusion of NH₃ (ammonia) from the colon into blood by lowering pH and forming non-diffusible NH₄ (ammonium)
    - serves as a substrate for incorporation of ammonia by bacteria, promotes growth in bowel lumen of bacteria which produce minimal ammonia
    - also acts as a laxative to eliminate nitrogen-producing bacteria from colon
  - if inadequate response with lactulose may try antibiotics
    - broad-spectrum antibiotics (metronidazole, rifaximin) eliminate ammonia producing bacteria from bowel lumen
    - non-absorbable antibiotic rifaximin probably most effective treatment but not readily available in Ontario
- best acute treatment in comatose patient is lactulose enemas

Ascites

Definition
- accumulation of excess fluid in the peritoneal cavity

Etiology

| Table 19. Serum-Ascites Albumin Gradient as an Indicator of the Causes of Ascites |
|---------------------------------|---------------------------------|
| Serum [Alb] – Ascitic [Alb] >11 g/L (1.1 g/dL) | Serum [Alb] – Ascitic [Alb] <11 g/L (1.1 g/dL) |
| Portal Hypertension Related | Non-Portal Hypertension Related |
| Cirrhosis/severe hepatitis | Peritoneal carcinomatosis |
| Chronic hepatic congestion (right heart failure, Budd-Chiari) | TB |
| Massive liver metastases | Pancreatic disease |
| Myxedema | Serositis |
| | Nephrotic syndrome* |

* In nephrotic syndrome: decreased serum [Alb] to begin with therefore gradient not helpful

Pathophysiology
- key factor in pathogenesis is increased sodium (and water) retention by the kidney for reasons not fully understood. Theories include:
  - underfill hypothesis: first step in ascites formation is increased portal pressure and low oncotic pressure (e.g. low serum albumin) driving water out of the splanchic portal circulation into abdominal cavity; the resulting decreased circulating volume causes secondary sodium retention by the kidney
  - overfill hypothesis: cirrhosis directly causes increased sodium retention by the kidney in the absence of hypovolemia and ascites arises secondarily
- peripheral arterial vasodilation theory (most popular): as portal HTN develops in cirrhosis, production of local mediators such as nitric oxide lead to splanchnic arterial vasodilation which ultimately results in reduction of effective arterial volume and compensatory sodium and fluid retention by the kidneys (i.e. circulation volume is increased, as per overflow hypothesis, but relatively underfilled, as per underfill hypothesis)

**Diagnosis**
- abdominal ultrasound
- physical exam (clinically detectable when >500 mL)
  - bulging flanks, shifting dullness, fluid-wave test positive
- most sensitive symptom: ankle swelling

**Investigations**
- diagnostic paracentesis
  - 1st aliquot: cell count
  - 2nd aliquot: chemistry (especially albumin, but also total protein; amylase if pancreatitis; TG and chylomicrons if turbid and suspect chylous ascites)
  - 3rd aliquot: C&S, Gram stain
  - 4th aliquot: cytology (usually positive in peritoneal carcinomatosis)

**Treatment**
- non-refractory ascites
  - Na+ restriction (daily sodium intake <2 g)
  - diuretics: spironolactone, furosemide
  - aim for weight loss 0.5-1 kg/d, more if concomitant peripheral edema (which is mobilized quicker than ascitic fluid); overly rapid weight loss increases risk of renal failure
  - double diuretic dose every 2-4 wk to achieve weight loss target
- refractory ascites (diuretics are inadequate or not tolerated)
  - therapeutic paracentesis with intravenous albumin paracentesis
- TIPS in an appropriate patient (no contraindications) with potential transplant-free survival advantage
- liver transplantation should be considered in every case, since development of ascites in patients with cirrhosis is associated with 50% 2 yr mortality

**Complication: Primary/Spontaneous Bacterial Peritonitis**
- primary/spontaneous bacterial peritonitis (SBP)
  - complicates ascites, but does not cause it (occurs in 10% of cirrhotic ascites); higher risk in patients with GI bleed
  - 1/3 of patients are asymptomatic, thus do not hesitate to do a diagnostic paracentesis in ascites even if no clinical indication of infection
  - fever, chills, abdominal pain, ileus, hypotension, worsening encephalopathy, acute kidney injury
  - Gram-negatives compose 70% of pathogens: E. coli (most common), Streptococcus, Klebsiella
  - diagnosis
    - absolute neutrophil count in peritoneal fluid >0.25x10⁹ cells/L (250 cells/mm³)
    - Gram stain positive in only 10-50% of patients
    - culture positive in <80% of patients (not needed for diagnosis)
  - prophylaxis: consider in patients with
    - cirrhosis or GI bleed: ceftriaxone IV daily or norfloxacin bid x 7 d
    - previous episode of SBP: long-term prophylaxis with daily norfloxacin or TMP-SMX
  - treatment
    - IV antibiotics (cefotaxime 2 g IV q8h or ceftriaxone 2g IV daily is the treatment of choice for 5 d; modify if response inadequate or culture shows resistant organisms)
    - IV albumin (1.5 g/kg at time of diagnosis and 1 g/kg on day 3) decreases mortality by lowering risk of acute renal failure

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**Biliary Tract**

**Jaundice**
- see Table 2, G6 and Figures 15 and 16, G42

**Signs and Symptoms**
- dark urine, pale stools: suggests that bilirubin elevation is from direct fraction
- pruritus: suggests chronic disease, cholestasis
- abdominal pain: suggests biliary tract obstruction from stone or pancreatic tumour (obstructive jaundice)
- painless jaundice in the elderly: think of pancreatic cancer, although most patients with pancreatic cancer have pain
- kernicterus: rarely seen in adults due to maturation of blood brain barrier
Investigations
• blood work: CBC, bilirubin (direct and total), liver enzymes (AST, ALT, ALP, GGT), liver function tests (INR/PT, PTT, albumin), amylase
• U/S or CT for evidence of bile duct obstruction (e.g. bile duct dilation)
• direct bile duct visualization
  ▪ magnetic resonance cholangiopancreatography (MRCP): non-invasive
  ▪ endoscopic ultrasound (EUS): sensitive for stones and pancreatic tumours
  ▪ endoscopic retrograde cholangiopancreatography (ERCP): invasive, most accurate, allows for therapeutic intervention
  ▪ percutaneous transhepatic cholangiography (PTC): if ERCP fails (endoscopic access not possible)

Figure 14. Approach to jaundice

Gilbert’s Syndrome

Definition
• mild decrease in glucuronyltransferase activity leading to defective conjugation of bilirubin
• an abnormality of bilirubin metabolism with no clinical relevance

Etiology/Epidemiology
• some patients have decreased hepatobiliary uptake
• affects 7% of population, especially males
• autosomal dominant, 70% due to a mutation in the UGT gene

Clinical Features
• presents in teens-20s, often an incidental finding
• only manifestation is intermittent jaundice with increased serum unconjugated bilirubin developing most characteristically while fasting, or at times of acute illness; no other clinical implications

Treatment
• none indicated (entirely benign)

Sclerosing Cholangitis

Definition
• narrowing of biliary tree (intra and/or extrahepatic bile ducts) from scarring

Etiology
• primary/idiopathic (most common)
  ▪ associated with IBD, more commonly UC, in up to 70% of patients (usually male)
  ▪ one of the most common indications for liver transplant
• secondary (less common)
  ▪ long-term choledocholithiasis
  ▪ cholangiocarcinoma
  ▪ surgical/traumatic injury (iatrogenic)
  ▪ contiguous inflammatory process
  ▪ post-ERCP
  ▪ associated with HIV/AIDS ("HIV cholangiopathy")
  ▪ IgG4-related disease

Signs and Symptoms
• often insidious, may present with fatigue and pruritus
• may present with signs of episodic bacterial cholangitis secondary to biliary obstruction

Investigations
• increased ALP (hallmark), less often increased bilirubin
• mildly increased AST, usually <300 U/L
• p-ANCA (30-80%), elevated IgM (40-50%)
• ERCP shows narrowing and dilatations of bile ducts that may result in "beading", both intrahepatic and extrahepatic bile ducts
  ▪ if intrahepatic narrowing only, do anti-mitochondrial antibody to rule out PBC

Complications
• repeated bouts of cholangitis may lead to complete biliary obstruction with resultant secondary biliary cirrhosis and hepatic failure
• increased incidence of cholangiocarcinoma (10-15%): difficult to diagnose and treat

Treatment
• image bile duct (MRCP) at least annually for early detection of cholangiocarcinoma (controversial)
• endoscopic sphincterotomy, biliary stent in selected cases of dominant CBD stricture
• antibiotics for cholangitis
• suppurative cholangitis requires emergency drainage of pus in CBD
• liver transplantation appears to be the best treatment for advanced sclerosing cholangitis (nearly 90% 1-yr survival; mean follow-up from time of diagnosis to need for transplant is 10 yr)
• ursodiol: previously recommended, but studies suggest that at least in high doses it increases mortality

Prognosis
• unfavourable regardless of treatment
• mean survival after diagnosis remains 4-10 yr

Primary Biliary Cirrhosis

Definition
• chronic inflammation and fibrous obliteration of intrahepatic bile ductules

Etiology/Epidemiology
• likely autoimmune (associated with Sjögren's syndrome, scleroderma, CREST syndrome, RA, thyroiditis)
• affects mainly middle-aged women (M:F = 1:9)

Signs and Symptoms
• often asymptomatic
• initial symptoms: pruritus, fatigue
• chronic: jaundice and melanosis (darkening skin) and other signs of cholestasis
• end-stage: hepatocellular failure, portal HTN, ascites
• high incidence of osteoporosis

Investigations
• increased ALP, GGT; bilirubin rises in later stage
• positive anti-mitochondrial antibodies (AMA; 95% specificity and sensitivity)
• increased serum cholesterol (mild increase in LDL, larger increase in HDL)
  ▪ may have: xanthelasmas, xanthomas
• liver biopsy confirms diagnosis and stages severity
• normal bile duct on MRCP rules out bile duct obstruction which can mimic PBC
• recently described "overlap" syndromes with autoimmune cholangitis, autoimmune hepatitis, sclerosing cholangitis
**Treatment**
- treat with ursodiol (less frequently colchicine, methotrexate)
- cholestyramine (for pruritus and hypercholesterolemia)
- calcium and vitamin D for low bone density; bisphosphonates if osteoporosis severe
- monitor for thyroid disease
- liver transplant if disease severe, progressive

**Prognosis**
- can be fatal, although not all asymptomatic patients show progression

**Table 20. Primary Sclerosing Cholangitis vs. Primary Biliary Cirrhosis**

<table>
<thead>
<tr>
<th></th>
<th>Primary Sclerosing Cholangitis</th>
<th>Primary Biliary Cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominant Gender</strong></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>Associated Comorbidities</strong></td>
<td>IBD, especially UC</td>
<td>Other autoimmune disorders (Sjögren’s, CREST, RA)</td>
</tr>
<tr>
<td><strong>Affected Ducts</strong></td>
<td>Both intra- and extra-hepatic</td>
<td>Intrahepatic only</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>ERCP/MRCP (narrowing and dilatations of ducts visualized)</td>
<td>Anti-mitochondrial antibodies, IgM, increased lipids, liver biopsy (absence of duct narrowing on ERCP)</td>
</tr>
</tbody>
</table>

**Secondary Biliary Cirrhosis**

**Definition**
- cirrhosis from prolonged partial or total obstruction of major bile ducts

**Etiology**
- acquired: post-operative strictures, chronic pancreatitis, sclerosing cholangitis, stone in bile duct
- congenital: CF, congenital biliary atresia, choledochal cysts

**Investigations**
- cholangiography and liver biopsy

**Treatment**
- treat obstruction, give antibiotics for cholangitis prophylaxis

**Biliary Colic, Cholecystitis**
- see **General Surgery**, GS48

**Ascending Cholangitis**
- see **General Surgery**, GS50

**Definition**
- infection of the biliary tree

**Etiology**
- stasis in the biliary tract due to obstruction or stricture (usually from previous cholecystectomy)
- infection originates in the duodenum or spreads hematogenously from the portal vein
- bacteria
  - *E. coli*, Klebsiella, Enterobacter, Enterococcus
  - co-infection with Bacteroides and Clostridia can occur

**Signs and Symptoms**
- Charcot’s triad: fever, RUQ pain, jaundice (50-70%)
- Reynolds Pentad in patients with suppurative cholangitis: fever, RUQ pain, jaundice, hypotension, altered mental status

**Investigations**
- increased WBC
- usually increased ALP and bilirubin, ALT variably elevated
- blood culture
- abdominal U/S: CBD dilation, stones
Treatment
- most important is drainage, ideally via ERCP, but if necessary by percutaneous biliary or surgical routes
- antibiotic therapy: broad spectrum to cover Gram-negatives, *Enterococcus*, and anaerobes (especially if CBD manipulation); no clear consensus on antibiotic choice but consider:
  - ampicillin + sulbactam or piperacillin/tazobactam
  - metronidazole + 3rd generation cephalosporin (e.g. ceftiraxone) or fluoroquinolone (e.g. ciprofloxacin or levofloxacin)
  - carbapenem monotherapy (e.g. imipenem or meropenem)

Prognosis
- good with effective drainage and antibiotics in mild to moderate cases
- high mortality (~50%) in patients with Reynolds Pentad

Pancreas

Pancreatic Enzyme Abnormalities

Causes of Increased Serum Amylase
- pancreatic disease
  - pancreatitis, pancreatic duct obstruction (e.g. ampullary cancer), pseudocyst, abscess, ascites, trauma, cancer
- non-pancreatic abdominal disease
  - biliary tract disease, bowel obstruction/ischemia, perforated or penetrating ulcer, ruptured ectopic pregnancy, aneurysm, chronic liver disease, peritonitis
- non-abdominal disease
  - cancer (lung, ovary, esophagus, etc.), salivary gland lesions, bulimia, renal transplant/insufficiency, burns, ketoacidosis
  - macroamylasemia

Causes of Increased Serum Lipase
- pancreatic disease: same as above
- non-pancreatic abdominal disease (mild elevations only): same as above
- non-abdominal disease
  - macrolipasemia
  - renal failure

Acute Pancreatitis

Etiology
Idiopathic: thought to be hypertensive sphincter or microlithiasis
Gallstones (45%)
Ethanol (35%)
Tumours: pancreas, ampulla, choledochocoele
Scorpion stings
Microbiological
  - bacterial: *Mycoplasma, Campylobacter, TB, M. avium intracellulare*, Legionella, leptospirosis
  - viral: mumps, rubella, varicella, viral hepatitis, CMV, EBV, HIV, Coxsackie virus, echovirus, adenovirus
  - parasites: ascariasis, clonorchiasis, echinococcosis
Autoimmune: SLE, polyarteritis nodosa (PAN), Crohn's disease
Surgery/trauma
  - manipulation of sphincter of Oddi (e.g. ERCP), post-cardiac surgery, blunt trauma to abdomen, penetrating peptic ulcer
Hyperlipidemia (TG >11.3 mmol/L; >1000 mg/dL), Hypercalcemia, Hypothermia
Emboli or ischemia
Drugs/toxins
  - azathioprine, mercaptopurine, furosemide, estrogens, methyl dopa, H2-blockers, valproic acid, antibiotics, acetaminophen, salicylates, methanol, organophosphates, steroids (controversial)

Pathophysiology
- activation of proteolytic enzymes within pancreatic cells, starting with trypsin, leading to local and systemic inflammatory response
- in gallstone pancreatitis, this is due to mechanical obstruction of the pancreatic duct by stones
• in ethanol-related pancreatitis, pathogenesis is unknown
• in rare genetic diseases, mutations prevent the physiological breakdown of trypsin required normally to stop proteolysis (e.g. mutant trypsin in hereditary pancreatitis or mutation in SPINK 1 gene which normally inhibits activated trypsin); may be model for ethanol-related pancreatitis

Pathology
• mild (interstitial)
  ▪ peri-pancreatic fat necrosis
  ▪ interstitial edema
• severe (necrotic)
  ▪ extensive peri-pancreatic and intra-pancreatic fat necrosis
  ▪ parenchymal necrosis and hemorrhage → infection in 60%
  ▪ release of toxic factors into systemic circulation and peritoneal space (causes multi-organ failure)
  ▪ severity of clinical features may not always correlate with pathology
  ▪ 3 phases
    ▪ local inflammation + necrosis → hypovolemia
    ▪ systemic inflammation in multiple organs, especially in lungs, usually after IV fluids given → pulmonary edema
    ▪ local complications 2 wk after presentation → pancreatic sepsis/abscess

Signs and Symptoms
• pain: epigastric, noncolicky, constant
• can radiate to back
• may improve when leaning forward
  (Ingelfinger’s sign)
• tender rigid abdomen; guarding
• N/V
• abdominal distention from paralytic ileus
• fever: chemical, not due to infection
• jaundice: compression or obstruction of bile duct
• Cullen’s/Grey-Turner’s signs
• tetany: transient hypocalcemia
• hypovolemic shock: can lead to renal failure
• acute respiratory distress syndrome
• coma

Investigations
• increased serum pancreatic enzymes: amylase, lipase (more specific)
• ALT >150 specific for biliary cause
• increased WBC, glucose, low calcium
• imaging: CT most useful for diagnosis and prognosis
  ▪ x-ray: “sentinel loop” (dilated proximal jejenum), calcification, and “colon cut-off sign” (colonic spasm)
  ▪ U/S: useful for evaluating biliary tree (67% sensitivity, 100% specificity)
  ▪ CT scan with IV contrast: useful for diagnosis and prognosis because contrast seen only in viable pancreatic tissue, non-viable areas can be biopsied percutaneously to differentiate sterile from infected necrosis
  ▪ ERCP or MRCP if cause uncertain, assess for duct stone, pancreatic or ampullary tumour, pancreas divisum

Classification
• interstitial edematous vs. necrotizing
• mild, moderate, severe

Prognosis
• usually a benign, self-limiting course, single or recurrent
• occasionally severe leading to
  ▪ shock
  ▪ pulmonary edema
  ▪ multi-organ dysfunction syndrome
  ▪ GI ulceration due to stress
  ▪ death
• numerous scales to describe severity: probably most useful is proportion of pancreas not taking up contrast on CT done 48 hours after presentation (necrotic pancreas does not take up the contrast dye)
• presence of organ failure, particularly organ failure that persists > 48 hours, is associated with worse outcomes

<table>
<thead>
<tr>
<th>Signs and Symptoms</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Jaundice</td>
</tr>
<tr>
<td>Radiate to back</td>
<td>Cullen’s/Grey-Turner’s signs</td>
</tr>
<tr>
<td>May improve</td>
<td>Tetany: transient hypocalcemia</td>
</tr>
<tr>
<td>Leaning forward</td>
<td>Hypovolemic shock: can lead to renal failure</td>
</tr>
<tr>
<td>Abdominal distention</td>
<td>Acute respiratory distress syndrome</td>
</tr>
<tr>
<td>Fever: chemical, not due to infection</td>
<td>Coma</td>
</tr>
</tbody>
</table>

Table 21. Collections in pancreatitis (Revised 2012 Atlanta Classification)

<table>
<thead>
<tr>
<th>Liquid</th>
<th>Solid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute peripancreatic fluid collection (APFC)</td>
<td>Acute necrotic collection (ANC)</td>
</tr>
<tr>
<td>Pancreatic pseudocyst</td>
<td>Walled-off necrosis (WON)</td>
</tr>
</tbody>
</table>

All of these collections are classified as infected or not infected

G45 Gastroenterology Pancreas
Toronto Notes 2016
Treatment
• goals (only supportive therapy available)
  1. hemodynamic stability
  2. analgesia
  3. oxygen
  4. stop progression of damage (difficult)
  5. treat local and systemic complications
• antibiotics controversial except in documented infection (use cephalosporins, imipenem)
• aspirate necrotic areas of pancreas to diagnose infection; drain if infected
• IV fluids (crystalloid or colloid)
  • beware third spacing of fluid, monitor urine output carefully
• NG suction (lets pancreas rest) if vomiting, stomach very dilated
• endoscopic sphincterotomy if severe gallstone pancreatitis (i.e. cholangitis or ongoing obstruction)
• nutritional support: nasojejunal feeding tube or TPN if cannot tolerate enteric feeds
  • recent evidence supports nasogastric enteral (or oral if feasible) feeds
• no benefit: glucagon, atropine, aprotinin, H2-blockers, peritoneal lavage
• follow clinically and CT/ultrasound to exclude complications
• chief role of surgery is to excise necrotic tissue (necrosectomy) in the case of infected pancreatic necrosis (try to delay for >2 wk to allow demarcation between viable and necrotic tissue)

Late Complications
• pseudocysts: follow if asymptomatic, drain if symptomatic or growing
  • drain: choice of endoscopic, percutaneous under radiological guidance, or surgical
• infected necrosis/abcesses: antibiotics + percutaneous drainage, endoscopic vs. surgical
• bleeding: (1) gastric varices if splenic vein thrombosis, (2) pseudoaneurysm of vessels in areas of necrosis, especially splenic artery, (3) duodenal ulcer related to compression of duodenum by enlarged pancreas
• splenic and portal vein thrombosis: no effective therapy described, anticoagulation not proven, hazardous
• rare: DM, pancreatic duct damage

Chronic Pancreatitis

Definition
• irreversible damage to pancreas characterized by
  1. pancreatic cell loss (from necrosis)
  2. inflammation
  3. fibrosis

Etiology/Pathophysiology
• alcohol (most common)
  • causes a larger proportion (>90%) of chronic pancreatitis than acute pancreatitis
  • changes composition of pancreatic juice (e.g. increases viscosity)
  • decreases pancreatic secretion of pancreatic stone protein (lithostathine) which normally solubilizes calcium salts
  • precipitation of calcium within pancreatic duct results in duct and gland destruction
  • toxic effect on acinar and duct cells – directly or via increasing free radicals
  • acinar cell injury leads to cytokine release, which stimulates pancreatic stellate cells to form collagen (leading to fibrosis)
  • varying degrees of ductular dilatation, strictures, protein plugs, calcification
• no satisfactory theory to explain why only a minority of alcoholics develop pancreatitis
• unusual causes
  • CF
  • severe protein-calorie malnutrition
  • hereditary
  • idiopathic

Signs and Symptoms
• early stages
  • recurrent attacks of severe abdominal pain (upper abdomen and back)
  • chronic painless pancreatitis: 10%
• late stages: occurs in 15% of patients
  • malabsorption syndrome when >90% of function is lost, steatorrhea
  • diabetes, calcification, jaundice, weight loss, pseudocyst, ascites, GI bleed
**Investigations**
- laboratory
  - increase in serum glucose
  - increase in serum ALP, less commonly bilirubin (jaundice)
  - serum amylase and lipase usually normal
- AXR: pancreatic calcifications
- U/S or CT: calcification, dilated pancreatic ducts, pseudocyst
- MRCP or ERCP: abnormalities of pancreatic ducts-narrowing and dilatation
- EUS: abnormalities of pancreatic parenchyma and pancreatic ducts, most sensitive test
- 72-h fecal fat test: measures exocrine function
- secretin test: gold standard, measures exocrine function but difficult to perform, unpleasant for patient, expensive
- fecal pancreatic enzyme measurement (elastase-1, chymotrypsin): available only in selected centres

**Treatment**
- most common problem is pain, difficult to control
- general management
  - total abstinence from alcohol
  - enzyme replacement may help pain by resting pancreas via negative feedback
  - analgesics
  - celiac ganglion blocks
  - time: pain decreases with time as pancreas "burns out"
- endoscopy: sphincterotomy, stent if duct dilated, remove stones from pancreatic duct
- surgery: drain pancreatic duct (pancreaticojejunostomy) if duct dilated (more effective than endoscopy); resect pancreas if duct contracted
- steatorrhea
  - pancreatic enzyme replacement
  - restrict fat, increase carbohydrate and protein (may also decrease pain)
  - neither endoscopy nor surgery can improve pancreatic function

**Autoimmune Pancreatitis**
- most commonly presents as a mimicker of pancreatic cancer (pancreatic mass detected because of jaundice ± abdominal pain)

**Investigations**
- histology: lymphocyte and plasma cell infiltration of pancreas
- imaging: focal or diffuse enlargement of pancreas on CT or MRI, sausage shaped, low density rim around pancreas
- serology: increased serum IgG4
- other organ involvement: sialadenitis, retroperitoneal fibrosis, biliary duct narrowing, nephritis

**Treatment**
- responds to prednisone

---

**Clinical Nutrition**

**Determination of Nutritional Status**
- corrected weight loss (expressed as body mass index [kg/m²]) is most important parameter in assessing need for nutritional support
- Subjective Global Assessment: simple bedside tool to assess nutritional status, to help identify those who will benefit from nutritional support

**Investigations**
- plasma proteins: albumin, pre-albumin (shorter half life than albumin), transferrin
  - decrease may indicate decreased nutritional status or disease state
- thyroid-binding globulin, retinol-binding protein (may be too sensitive)
- anthropometry (e.g. triceps skinfold thickness), grip strength less often used

**Table 22. Areas of Absorption of Nutrients**

<table>
<thead>
<tr>
<th></th>
<th>Fe</th>
<th>CHO</th>
<th>Proteins, Lipids</th>
<th>Bile Acids</th>
<th>Vit B12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenum</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Jejunum</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ileum</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>
Enteral Nutrition

Definition
- enteral nutrition (tube feeding) is a way of providing food through a tube placed in the stomach or the small intestine
- choice of tubes: nasogastric (NG), nasojejunal (NJ), percutaneous endoscopic gastrostomy (“G-tube” or “PEG tube”), percutaneous endoscopic jejunostomy (“J-tube”) or tubes can be placed radiologically, surgically

Indications
- oral feeding inadequate or contraindicated

Feeds
- polymeric feeds contain whole protein, carbohydrate, fat as a liquid, with or without fibre
- elemental feeds contain protein as amino acids, carbohydrate as simple sugars, fat content low (therefore high osmolarity)
- specific diets: low carbohydrate/high fat solution for ventilated patients (carbohydrate has a high respiratory quotient so minimizes carbon dioxide production), high energy, low electrolyte solutions for dialysis patients

Relative Contraindications
- non-functioning gut (e.g. intestinal obstruction, enteroenteral or entero-cutaneous fistulae)
- uncontrolled diarrhea
- GI bleeding

Complications
- aspiration
- diarrhea
- refeeding syndrome (rare): carbohydrate can stimulate excessive insulin release, leading to cellular uptake and low serum levels of phosphate, magnesium, potassium
- overfeeding syndrome (rare): hypertonic dehydration, hyperglycemia, hypercapnea, azotemia (from excess protein)

Enteral Nutrition Advantages over Parenteral Nutrition
- fewer serious complications (especially sepsis)
- nutritional requirements for enterally administered nutrition better understood
- can supply gut-specific fuels such as glutamine and short chain fatty acids
- nutrients in the intestinal lumen prevent atrophy of the gut and pancreas
- prevents gallstones by stimulating gallbladder motility
- much less expensive

Parenteral Nutrition

Definition
- parenteral nutrition (PN) is the practice of feeding a person intravenously, bypassing the usual process of eating and digestion

Indications
- short-term (<1 mo)
  - whenever GI tract not functioning
  - only situations where PN has been well shown to increase survival are after bone marrow transplant and in short bowel syndrome, some evidence for benefit in gastric cancer, but often used in ICU, perioperatively, and in difficult to control sepsis
  - pre-operative: only useful in severely malnourished (e.g. loss of >15% of pre-morbid weight, serum albumin <28 g/L or <2.8 g/dL), and only if given for ≥2 wk
  - renal failure: PN shown to increase rate of recovery; no increase in survival
  - liver disease: branched chain amino acids may shorten duration of encephalopathy; no increase in survival
  - IBD: PN closes fistulae and heals acute exacerbations of mucosal inflammation, but effect is transient (EN is equally effective)
  - some evidence for efficacy, but convincing data not available for
    - radiation/chemotherapy-induced enteritis
    - AIDS with wasting diarrhea
  - severe acute pancreatitis
- long-term (>1 mo): can be given at home
  - severe untreatable small bowel disease (e.g. radiation enteritis, extensive CD, high output fistulae)
  - following surgical resection of >70% of small bowel (e.g. small bowel infarction)
  - severe motility diseases (e.g. scleroderma affecting bowel)

Whenever possible, enteral nutrition is ALWAYS preferable over parenteral nutrition
Relative Contraindications
- functional GI tract for enteral nutrition
- active infection; at least until appropriate antibiotic coverage
- inadequate venous access; triple-lumen central venous lines usually prevent this problem
- unreliable patient or clinical setting

Complications of PN
- sepsis: most serious of the common complications
- mechanical pneumothorax from insertion of central line, catheter migration and thrombosis, air embolus
- metabolic: CHF, hyperglycemia, gallstones, cholestasis

### Common Medications

#### Table 23. Common Drugs Prescribed in Gastroenterology

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proton Pump Inhibitors</td>
<td>omeprazole</td>
<td>Losec®/Prilosec®</td>
<td>20 mg PO OD</td>
<td>Inhibits gastric enzymes H⁺/K⁺-ATPase (proton pump)</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, reflux esophagitis, symptomatic GERD, dyspepsia, Zollinger-Ellison syndrome, eradication of H. pylori (combined with antibiotics)</td>
<td>Hypersensitivity to drug</td>
<td>Dizziness, headache, flatulence, abdominal pain, nausea, rash, increased risk of osteoporotic fracture (secondary to impaired calcium absorption)</td>
</tr>
<tr>
<td></td>
<td>lansoprazole or</td>
<td>Prevacid®</td>
<td>Oral therapy: lansoprazole 15-30 mg OD (before breakfast), dexlansoprazole 30-60mg OD (does not need to be taken before breakfast)</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>dexlansoprazole</td>
<td>Dexilant®</td>
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<td></td>
<td>pantoprazole</td>
<td>Pantoloc®/Protonix®</td>
<td>40 mg PO OD for UGB: 80 mg IV bolus then 8 mg/h infusion</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
<td>Same as above</td>
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<tr>
<td></td>
<td>rabeprazole</td>
<td>Pariet®/Aciphex®</td>
<td>40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>esomeprazole</td>
<td>Nexium®</td>
<td>20-40 mg PO OD</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
<td>Same as above</td>
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<tr>
<td></td>
<td>esomeprazole</td>
<td>Nexium®</td>
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<tr>
<td>Histamine H₂-Receptor</td>
<td>ranitidine</td>
<td>Zantac®</td>
<td>300 mg PO OD or 150 mg bid IV therapy: 50 mg q8h (but tachyphylaxis a problem)</td>
<td>Inhibits gastric histamine H₂-receptors</td>
<td>Duodenal ulcer, gastric ulcer, NSAID-associated gastric and duodenal ulcers, ulcer prophylaxis, reflux esophagitis, symptomatic GERD; not useful for acute GI bleeds</td>
<td>Hypersensitivity to drug</td>
<td>Confusion, dizziness, headache, arrhythmias, constipation, nausea, agranulocytosis, pancytopenia, depression</td>
</tr>
<tr>
<td>Antagonists</td>
<td>famotidine</td>
<td>Pepcid®</td>
<td>Oral therapy: duodenal/gastric ulcers: 40 mg qhs GcERD: 20 mg bid IV therapy: 20 mg bid</td>
<td>Same as above</td>
<td>Same as above and UGB</td>
<td>Same as above</td>
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<tr>
<td>Stool Softener</td>
<td>docusate sodium</td>
<td>Colace®</td>
<td>100-400 mg PO OD, divided in 1-4 doses</td>
<td>Promotes incorporation of water into stool</td>
<td>Relief of constipation</td>
<td>Presence of abdominal pain, fever, N/V</td>
<td>Throat irritation, abdominal cramps, rashes</td>
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<td></td>
<td>lactulose</td>
<td>Lactulose/Constulose®</td>
<td>15-30 ml PO OD to bid Encephalopathy: 15-30 mL bid to qid</td>
<td>Poorly absorbed in GI tract and is broken down by colonic bacteria into lactic acid in the colon, increases osmotic colonic contents, increases stool volume</td>
<td>Chronic constipation, prevention, and treatment of portal-systemic encephalopathy</td>
<td>Patients who require a low galactose diet</td>
<td>Flatulence, intestinal cramps, nausea, diarrhea if excessive dosage</td>
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<tr>
<td></td>
<td>PEG3350</td>
<td>Lax-a-day®/Golytely®</td>
<td>Constipation: 17 g powder dissolved in 4-8 oz liquid PO OD</td>
<td>Osmotic agent causes water retention in stool and promotes frequency of stool</td>
<td>Relief of constipation Colonoscopy prep</td>
<td>Hypersensitivity to drug</td>
<td>Abdominal distension, pain, anal pain, thirst, nausea, rigor, tonic-clonic seizures (rare)</td>
</tr>
</tbody>
</table>
Table 23. Common Drugs Prescribed in Gastroenterology (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
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<tbody>
<tr>
<td>Stimulant Laxatives</td>
<td>senna</td>
<td>Senokot®</td>
<td>Tablets: 1-4 PO qhs, Syrup: 10-15 mL PO qhs</td>
<td>Induce peristalsis in lower colon</td>
<td>Constipation</td>
<td>Patients with acute abdomen</td>
<td>Abdominal cramps, discoloration of breast milk, urine, feces, melanosis coli and atonic colon from prolonged use (controversial)</td>
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<td>bisacodyl</td>
<td>Bisacodyl®</td>
<td>5-30 mg PO OD (start at 10 mg for bowel preparation)</td>
<td>Enteric nerve stimulation and local contact-induced secretory effects. Colonic movements</td>
<td>Constipation, Preparation of bowel for procedure</td>
<td>GI obstruction</td>
<td>Gastroenteritis, Abdominal colic, abdominal discomfort, pruritus (with suppository use), diarrhea</td>
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<tr>
<td>Bulk Laxatives</td>
<td>psyllium</td>
<td>Metamucil®</td>
<td>2-6 tabs (1 tab = 0.52 g) PO od-tid prn</td>
<td>Increases stool bulk → water retention in stool</td>
<td>Constipation</td>
<td>Hypersensitivity to drug</td>
<td>GI obstruction, diarrhea, constipation, abdominal cramps</td>
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<tr>
<td>Antidiarrheal Agents</td>
<td>loperamide</td>
<td>Imodium®</td>
<td>Acute diarrhea: 4 mg PO initially, followed by 2 mg after each unformed stool</td>
<td>Acts as antidiarrheal via cholinergic, noncholinergic, opiate, and nonopiate receptor-mediated mechanisms; decreases activity of myenteric plexus</td>
<td>Adjunctive therapy for acute non-specific diarrhea, chronic diarrhea associated with IBD and for reducing the volume of discharge for ileostomies, colostomies, and other intestinal resections</td>
<td>Children &lt; 2 yr, known hypersensitivity to drug, acute dysentery characterized by blood in stools and fever, acute ulcerative colitis or pseudomembranous colitis associated with broad-spectrum antibiotics</td>
<td>Abdominal pain or discomfort, drowsiness or dizziness, tiredness, dry mouth, nausea and vomiting, hypersensitivity reaction</td>
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<td>diphenoxylate/atropine</td>
<td>Lomotil®</td>
<td>5 mg PO tid to qid</td>
<td>Inhibits GI propulsion via direct action on smooth muscle, resulting in a decrease in peristaltic action and increase in transit time</td>
<td>Adjunctive therapy for diarrhea, as above</td>
<td>Hypersensitivity to diphenoxylate or atropine, jaundice, pseudomembranous enterocolitis, diarrhea caused by enterotoxin producing bacteria</td>
<td>Dizziness, drowsiness, insomnia, headache, N/V, cramps, allergic reaction</td>
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<tr>
<td>Anti-Emetics</td>
<td>dimenhydrinate</td>
<td>Gravol®</td>
<td>25-50 mg PO/IM q4-6h pm</td>
<td>Competitive H1 receptor antagonist in GI tract, blood vessels, and respiratory tract. Blocks chemoreceptor trigger zone. Diminishes vestibular simulation and disrupts labyrinthine function through central anticholinergic action</td>
<td>Motion sickness, radiation sickness, postoperative vomiting, and drug-induced N/V</td>
<td>Hypersensitivity to drug</td>
<td>Xerostomia, sedation</td>
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<td></td>
<td>prochlorperazine</td>
<td>Stemetil®</td>
<td>5-10 mg PO/IM bid-tid pm</td>
<td>D1, D2 receptor antagonist in chemoreceptor trigger zone and a adrenergic and anti-cholinergic effects Depresses reticular activating system (RAS) affecting emesis</td>
<td>Post-operative N/V, antipsychotic, anxiety</td>
<td>Hypersensitivity to drug</td>
<td>Dystonia, EPS, seizure, neuroleptic malignant syndrome (NMS) (rarely)</td>
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<td></td>
<td>metoclopramide</td>
<td>Maxeran®</td>
<td>10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)</td>
<td>Dopamine and 5-HT receptor antagonist in chemoreceptor trigger zone. Enhances response to ACh in upper GI tract, enhancing motility and gastric emptying. Increases LES tone</td>
<td>GERD, diabetic gastroparesis, post-operative and chemotherapeutic induced N/V, migraines, constipation</td>
<td>Hypersensitivity to drug, GI obstruction, perforation, hemorrhage, phaeochromocytoma, seizures, and EPS</td>
<td>Restlessness, drowsiness, dizziness, fatigue, EPS, some rare serious side effects include NMS, agranulocytosis</td>
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<td></td>
<td>ondansetron</td>
<td>Zofran®</td>
<td>Depends on procedure, generally 8-16 mg PO</td>
<td>Selective 5HT3 receptor antagonist in central chemoreceptor trigger zone and peripherally on vagus nerve</td>
<td>N/V caused by cancer chemotherapy and radiation therapy; multiple off label uses, including gastroenteritis N/V</td>
<td>Morphine, hypersensitivity to drug</td>
<td>Constipation, diarrhea, increased liver enzymes, headache, fatigue, malaise, cardiac dysrhythmia</td>
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<tr>
<td></td>
<td>granisetron</td>
<td>Kytril®</td>
<td>1 mg PO bid (for nausea from chemotherapy/radiation)</td>
<td>Same as above</td>
<td>N/V caused by cancer chemotherapy and radiation therapy</td>
<td>Same as above</td>
<td>Constipation, prolonged QT interval (rarely)</td>
</tr>
</tbody>
</table>
Table 23. Common Drugs Prescribed in Gastroenterology (continued)

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing Mechanism</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IBD Agents</strong></td>
<td>mesalamine</td>
<td>Pentasa®, Salofalk®, Asacol®, Mesasal®</td>
<td>CD: 1 g PO tid/qid Active UC: 1 g PO qid Maintenance UC: 1.6 g PO divided doses daily also as suppositories and enemas</td>
<td>5-ASA: Blocks arachidonic acid metabolism to prostaglandins and leukotrienes</td>
<td>IBD</td>
<td>Hypersensitivity to mesalamine salicylates; Asacol contains phthalate, potential urogenital teratogenicity for male fetus</td>
<td>Abdominal pain, constipation, arthralgia, headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sulfasalazine</td>
<td>Salazopyrin®</td>
<td>3-4 g/d PO in divided doses</td>
<td>Compound composed of 5-ASA bound to sulfapyridine, hydrolysis by intestinal bacteria releases 5-ASA, the active component</td>
<td>Colonic disease</td>
<td>Hypersensitivity to sulfasalazine, sulfapyridine, salicylates; intestinal or urinary obstruction, porphyria</td>
<td>Rash, loss of appetite, N/V, headache, oligospermia (reversible)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>prednisone</td>
<td></td>
<td>20-40 mg PO OD for acute exacerbation</td>
<td>Anti-inflammatory</td>
<td>Mod-severe CD and UC</td>
<td>Complications of steroid therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immuno-suppressive Agents</strong></td>
<td>6-mercaptopurine (6-MP)</td>
<td>Purinethol®</td>
<td>CD: 1.5 mg/kg/d PO</td>
<td>Immunosuppressive</td>
<td>IBD: active inflammation and to maintain remission</td>
<td>Hypersensitivity to mercaptopurine, prior resistance to mercaptopurine or thioguanine, history of treatment with alkylating agents, hypersensitivity to azathioprine, pregnancy</td>
<td>Pancreatitis, bone marrow suppression, increased risk of cancer</td>
<td></td>
</tr>
<tr>
<td></td>
<td>azathioprine</td>
<td>Azasan®, Imuran®</td>
<td>IBD: 2-3 mg/kg/d PO</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
<td></td>
</tr>
<tr>
<td><strong>Immunomodulators</strong></td>
<td>infliximab</td>
<td>Remicade®</td>
<td>5-10 mg/kg IV over 2 h</td>
<td>Antibody to TNFα</td>
<td>Medically refractory CD</td>
<td>Heart failure, moderate to severe, doses &gt; 5 mg/kg</td>
<td>Reported cases of reactivated TB, PCP, lymphoma, other infections</td>
<td></td>
</tr>
</tbody>
</table>

**Landmark Gastroenterology Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>MELD</td>
<td>Gastroenterology 2003;124:91-6</td>
<td>MELD score can be applied for allocation of donor livers as it accurately predicts 3 mo mortality in patients with chronic liver failure</td>
</tr>
<tr>
<td>Inflliximab, azathioprine, or combination</td>
<td>NEJM 2010; 362:1383-95</td>
<td>In moderate-severe Crohn’s disease, infliximab + azathioprine was more likely to result in corticosteroid-free remission than infliximab monotherapy. Infliximab monotherapy was more effective than azathioprine monotherapy. Similar results have been reported for ulcerative colitis (Gastroenterology 2014; 146:392-400)</td>
</tr>
<tr>
<td>Enteral versus parenteral</td>
<td>Cochrane Database Syst Rev 2010;1</td>
<td>For acute pancreatitis, no trial was convincing alone, but in the congregate, enteral feeds via nasogastric tube is preferable to either no feeding or parenteral nutrition</td>
</tr>
<tr>
<td>Rifaximin treatment in hepatic encephalopathy</td>
<td>NEJM 2010; 362:1071-81</td>
<td>The most convincing of several articles establishing this non-absorbable antibiotic as the treatment of choice for hepatic encephalopathy for maintaining remission from hepatic encephalopathy and reducing hospitalization associated with the disease</td>
</tr>
<tr>
<td>Adenoma detection rate and risk of colorectal cancer and death</td>
<td>NEJM 2014; 370:1298-1306</td>
<td>A high miss rate for colorectal cancers has been suggested, chiefly in the right colon. This study demonstrates a method of assessing the competence of endoscopists in detecting cancers using adenoma detection rate (the proportion of colonoscopic exams in which a physician detects one or more adenomas) as a surrogate marker. Adenoma detection rate was associated with lower risk of interval colorectal cancer and has launched quality assurance programs for screening colonoscopies</td>
</tr>
<tr>
<td>Prednisolone or pentoxifylline for alcoholic hepatitis</td>
<td>NEJM 2015; 372:1619-28</td>
<td>For alcoholic hepatitis, prednisolone improved survival when the Maddrey’s discriminant function &gt; 32, but the benefit did not reach statistical significance and pentoxifylline was of no advantage at all. Other studies had shown some benefit with pentoxifylline, but this study was the most definitive</td>
</tr>
</tbody>
</table>
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Basic Anatomy Review

Figure 1. Abdominal incisions

Lateral Abdominal Wall Layers and their Continuous Spermatic and Scrotal Structures (superficial to deep)
1. skin (epidermis, dermis, subcutaneous fat)
2. superficial fascia
   - Camper's fascia (fatty) → Dartos fascia
   - Scarpa's fascia (membranous) → Colles' superficial perineal fascia
3. muscle (see Figure 2 and Figure 3)
   - external oblique → inguinal ligament → external spermatic fascia and spermatic cord
   - internal oblique → cremasteric muscle/fascia
   - transversus abdominis → posterior inguinal wall
4. transversalis fascia → internal spermatic fascia
5. preperitoneal fat
6. peritoneum → tunica vaginalis

Midline Abdominal Wall Layers (superficial to deep)
1. skin
2. superficial fascia
3. rectus abdominis muscle: in rectus sheath, divided by linea alba
   - anterior rectus sheath = external oblique aponeurosis and anterior leaf of internal oblique aponeurosis
   - posterior rectus sheath = posterior leaf of internal oblique aponeurosis and transversus abdominis aponeurosis
   - below arcuate line
   - aponeuroses of external oblique, internal oblique, transversus abdominis all pass in front of rectus abdominis
4. arteries: superior epigastric (branch of internal thoracic), inferior epigastric (branch of external iliac); both arteries anastomose and lie behind the rectus muscle (superficial to posterior rectus sheath above arcuate line)
5. transversalis fascia
6. peritoneum

Figure 2. Continuity of the abdominal wall with layers of the scrotum and spermatic cord
Figure 3. Midline cross-section of abdominal wall

Figure 4. Blood supply to the GI tract

Venous Flow

Figure 5. Venous drainage of the GI tract

Celiac trunk (1)
   i) Common hepatic artery (2)
      • Hepatic proper (3)
         – Left hepatic artery (4)
         – Right hepatic artery (5)
      • Right gastric artery (7)
   ii) Left gastric artery (6)
   iii) Splenic artery (9)

Superior mesenteric artery (10)
   i) Right colic artery (12)
   ii) Middle colic artery (11)
   iii) Ileocolic artery (13)
   iv) Ileal and jejunal branches (14)

Inferior mesenteric artery (15)
   i) Left colic artery (16)
   ii) Sigmoid arteries (17)
   iii) Superior rectal artery (18)

Porto-systemic anastomoses:
1. Esophageal branches of left gastric vein with esophageal veins
2. Paraumbilical veins with subcutaneous veins of anterior abdominal wall
3. Superior rectal vein with middle and inferior rectal veins

<table>
<thead>
<tr>
<th>Organ</th>
<th>Arteries</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Left and right hepatic branches of hepatic proper</td>
</tr>
<tr>
<td>Spleen</td>
<td>Splenic</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Cystic (branch of right hepatic artery)</td>
</tr>
<tr>
<td>Stomach</td>
<td>1. Lesser curvature: right and left gastric 2. Greater curvature: right (branch of gastroduodenal) and left (branch of splenic) gastropiploic 3. Fundus: short gastrics (branch of splenic)</td>
</tr>
<tr>
<td>Duodenum</td>
<td>1. Gastroduodenal 2. Pancreaticoduodenals (superior branch of gastroduodenal, inferior branch of superior mesenteric)</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1. Pancreatic branches of splenic 2. Pancreaticoduodenals</td>
</tr>
<tr>
<td>Small intestine</td>
<td>1. Superior mesenteric branches: jejunal, ileal, ileocolic</td>
</tr>
<tr>
<td>Large intestine</td>
<td>1. Superior mesenteric branches: right colic, middle colic 2. Inferior mesenteric branches: left colic, sigmoid, superior rectal</td>
</tr>
</tbody>
</table>
Differential Diagnoses of Common Presentations

Acute Abdominal Pain

- acute abdomen = severe abdominal pain of acute onset and requires urgent medical attention
- in patients with acute abdominal pain, the first diagnoses that you should consider are those requiring potential urgent surgical intervention
- two main patterns constituting urgent general surgery referrals are peritonitis and obstruction

<table>
<thead>
<tr>
<th>RUQ</th>
<th>EPICASTRIC</th>
<th>LUQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatobiliary</td>
<td>Cardiac</td>
<td>Pancreatic (acute vs. chronic)</td>
</tr>
<tr>
<td>Biliary colic</td>
<td>Aortic dissection/ruptured AAA</td>
<td>Pancreatic pseudocyst</td>
</tr>
<tr>
<td>Choledocholithiasis</td>
<td>Pericarditis</td>
<td>Pancreatic tumours</td>
</tr>
<tr>
<td>Cholangitis</td>
<td>Gastritis</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>CBD obstruction (stone, tumour)</td>
<td>GERD/esophagitis</td>
<td>Gastritis</td>
</tr>
<tr>
<td>Hepatitis</td>
<td>PUD</td>
<td>PUD</td>
</tr>
<tr>
<td>Budd-Chiari</td>
<td>Pancreatitis</td>
<td>Splenic flexure pathology</td>
</tr>
<tr>
<td>Hepatic abscess/mass</td>
<td>Mallory-Weiss tear</td>
<td>(e.g. CRC, ischemia)</td>
</tr>
</tbody>
</table>

DIFFUSE

Gastrointestinal
- Peritonitis
- Early appendicitis, perforated appendicitis
- Mesenteric ischemia
- Crohn’s disease
- Gastroenteritis/colitis
- Constipation
- Bowel obstruction
- Pancreatitis
- Inflammatory bowel disease
- Irritable bowel syndrome
- Ogilvie’s syndrome

Cardiovascular/Hematological
- Acute dissection/ruptured AAA
- Sickle cell crisis

Genitourinary/Gynecological
- Perforated ectopic pregnancy
- PID
- Acute urinary retention

Endocrinological
- Carcinoid syndrome
- Diabetic ketoacidosis
- Addisonian crisis
- Hypercalcaemia

Other
- Lead poisoning
- Tertiary syphils

SUPRAPUBIC

Gastrointestinal (see RLQ/LUQ)
- Acute appendicitis
- IBD

Gynecological
- Ecstatic pregnancy
- PID

Endometriosis
- Threatened/incomplete abortion
- Hydrosalpinx/salpingitis
- Ovarian torsion
- Hemorrhagic fibroid
- Tubo-ovarian abscess

Genitourinary
- Cystitis (infectious, hemorrhagic)
- Hydroureter/urinary colic
- Epididymitis
- Testicular torsion
- Acute urinary retention

Extraperitoneal
- Rectus sheath hematoma

In all patients presenting with an acute abdomen, order the following:

**KEY TESTS FOR SPECIFIC DIAGNOSIS**
- ALP, ALT, AST, bilirubin
- Amylase/lipase
- Urinalysis
- β-HCG (in women of childbearing age)
- Troponins
- Lactate

**KEY TESTS FOR OR PREPARATION**
- CBC, electrolytes, BUN, creatinine, glucose
- CXR + ECG
- INR/PTT

Types of Peritonitis
- Primary peritonitis: spontaneous without clear etiology
- Secondary peritonitis: due to a perforated viscus
- Tertiary peritonitis: recurrent secondary peritonitis more often with resistant organisms

Localization of Pain
Most digestive tract pain is perceived in the midline because of bilaterally symmetric innervation; kidney, ureter, ovary, or somatically innervated structures are more likely to cause lateralized pain

Referred Pain
- Biliary colic: to right shoulder or scapula
- Renal colic: to groin
- Appendicitis: periumbilical to right lower quadrant (RLQ)
- Pancreatitis: to back
- Ruptured aortic aneurysm: to back or flank
- Perforated ulcer: to RLQ (right paracolic gutter)
- Hip pain: to groin

Most Common Presentations of Surgical Pain
- Sudden onset with rigid abdomen = perforated viscus
- Pain out of proportion to physical findings = ischemic bowel
- Vague pain that subsequently localizes = appendicitis or other intra-abdominal process that irritates the parietal peritoneum
- Waves of colicky pain = bowel obstruction
## Abdominal Mass

### Table 2. Differential Diagnosis of Abdominal Mass

<table>
<thead>
<tr>
<th>Right Upper Quadrant (RUQ)</th>
<th>Upper Midline</th>
<th>Left Upper Quadrant (LUQ)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gallbladder:</td>
<td>Pancreas:</td>
<td>Spleen:</td>
</tr>
<tr>
<td>cholecystitis, cholangiocarcinoma, peri-ampullary malignancy, cholelithiasis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary tract:</td>
<td>pancreatic adenocarcinoma, other pancreatic neoplasm, pseudocyst</td>
<td></td>
</tr>
<tr>
<td>Klatskin tumour</td>
<td>Abdominal aorta: AAA (pulsatile)</td>
<td></td>
</tr>
<tr>
<td>Liver:</td>
<td>GI: gastric tumour (adenocarcinoma, gastrointestinal stromal tumour, carcinoid tumour), MALT lymphoma</td>
<td></td>
</tr>
<tr>
<td>Hepatomegaly, hepatitis, abscess, tumour (hepatocellular carcinoma, metastatic tumour, etc.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right Lower Quadrant (RLQ)</td>
<td>Lower Midline</td>
<td>Intestine:</td>
</tr>
<tr>
<td>Intestine: stool, tumour (CRC), mesenteric adenitis, appendicitis, appendiceal abscess or other abscess, typhilitis, intussusception, Crohn’s inflammation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ovary:</td>
<td>Intestine: stool, tumour, abscess (see RLQ)</td>
<td></td>
</tr>
<tr>
<td>Ovarian cyst, ectopic pregnancy, cyst (physiological vs. pathological), tumour (serous, mucinous, struma ovarii, germ cell, Krukenberg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fallopian tube: ectopic pregnancy, tubo-ovarian abscess, hydroosalpinx, tumour</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Gastrointestinal Bleeding

- see Gastroenterology, G25, G27

### Indications for Surgery

- failure of medical management
- exsanguinating hemorrhage: hemodynamic instability despite vigorous resuscitation
- recurrent hemorrhage after initial stabilization procedures with up to two attempts of endoscopic hemostasis
- hypovolemic shock
- prolonged bleeding with transfusion requirement >3 units
- bleeding at rate >1 unit/8 h

### Surgical Management of GI Bleeding

- **UGIB**
  - bleeding from a source proximal to the ligament of Treitz
  - often presents with hematemesis and melena unless very brisk (then can present with hematochezia, hypotension, tachycardia)
  - initial management with endoscopy; if fails, then consider surgery
  - note: PUD accounts for approximately 55% of severe UGIB
- **LGIB**
  - bleeding from a source distal to the ligament of Treitz
  - often presents with BRBPR unless proximal to transverse colon
  - may occasionally present with melena
  - initial management with colonoscopy to detect and potentially stop source of bleeding
  - 75% of patients will spontaneously stop bleeding, however if bleeding continues barium enema should NOT be performed
  - angiography, RBC scan to determine source as indicated
  - surgery indicated if bleeding is persistent - aimed at removing underlying cause of bleeding
  - obscure bleed may require blind total colectomy if the source is not found

### Table 3. Differential Diagnosis of GI Bleeding

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td>Excess anticoagulation (coumadin, heparin, etc.)</td>
</tr>
<tr>
<td></td>
<td>Excess antiplatelet ( clopidogrel, ASA)</td>
</tr>
<tr>
<td></td>
<td>DIC Congenital bleeding disorders</td>
</tr>
<tr>
<td>Nose</td>
<td>Epistaxis</td>
</tr>
<tr>
<td>Esophagus</td>
<td>Esophageal varices</td>
</tr>
<tr>
<td></td>
<td>Mallory-Weiss tear</td>
</tr>
<tr>
<td></td>
<td>Esophagitis</td>
</tr>
<tr>
<td>Stomach</td>
<td>Gastritis</td>
</tr>
<tr>
<td></td>
<td>Gastric varices</td>
</tr>
<tr>
<td></td>
<td>Dieulafoy’s lesion</td>
</tr>
<tr>
<td>Duodenum</td>
<td>Duodenal ulcer</td>
</tr>
<tr>
<td></td>
<td>Perforated duodenal ulcer*</td>
</tr>
<tr>
<td>Jejunum</td>
<td>Tumours*</td>
</tr>
<tr>
<td></td>
<td>Polyps</td>
</tr>
<tr>
<td></td>
<td>Ulcers</td>
</tr>
<tr>
<td></td>
<td>Aorto-esophageal fistula (generally post endovascular aortic repair)*</td>
</tr>
<tr>
<td></td>
<td>Esophageal cancer</td>
</tr>
<tr>
<td></td>
<td>Gastric ulcer</td>
</tr>
<tr>
<td></td>
<td>Gastric cancer*</td>
</tr>
<tr>
<td></td>
<td>Duodenal cancer*</td>
</tr>
</tbody>
</table>

Pancreatitis can look like a surgical abdomen, but is rarely an indication for immediate laparotomy

### Indications for Urgent Operation

- Overt bleeding: obvious hematochezia or melena per rectum visible to naked eye
- Occult bleeding: bleeding per rectum is not obvious to naked eye (e.g. positive guaiac test)
- Obstructed bleeding: overt bleeding with no identifiable source after colonoscopy and endoscopy

### Transfusion Strategies for Acute Upper Gastrointestinal Bleeding

NEJM 2013;368:11-21

Recent study by Villanueva et al., demonstrates that a restrictive transfusion strategy (transfusion with hemoglobin below 70 g/L) significantly improves outcomes in patients with acute UGIB, compared to a liberal transfusion strategy (transfusion with hemoglobin below 90 g/L). Refer to study for details.
Table 3. Differential Diagnosis of GI Bleeding (continued)

<table>
<thead>
<tr>
<th>Anatomical Source</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ileum and Ileocecal Junction</td>
<td>Crohn’s disease* Tuberculosis of ileocecal junction</td>
</tr>
<tr>
<td>Large Intestine</td>
<td>Crohn’s disease (less frequently presents with bleeding)* Pancolitis (infectious, chemotherapy, or radiation induced) Bleeding post-gastrointestinal anastomosis</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>Polyps *(if not amenable to colonoscopic polypectomy) Inflammatory bowel disease (IBD)</td>
</tr>
<tr>
<td>Rectum and Anus</td>
<td>Polyps <em>(if not amenable to colonoscopic polypectomy) Crohn’s or ulcerative colitis</em> Solitary rectal ulcer syndrome</td>
</tr>
</tbody>
</table>

*Managed surgically in most cases

**Jaundice**

- see Gastroenterology, G40

**Pre-Operative Preparations**

**Considerations**

- informed consent (see Ethical, Legal, and Organizational Medicine, ELOAM7?)
- screening questionnaire to determine risk factors e.g. age, exercise capacity, medication use, allergies
- consider pre-operative anesthesia, medicine consult as indicated to optimize patient status
- NPO according to guidelines (see Anesthesia and Perioperative Medicine, A5)
- IV – balanced crystalloid at maintenance rate (4:2:1 rule → roughly 100-125 cc/h): normal saline or Ringer’s lactate; bolus to catch up on estimated losses including losses from bowel prep
  - appropriate use of fluids perioperatively decreases risk of cardiorespiratory complications
- patient’s regular medications including with the exception of hypoglycemic agents, diuretics and ACE-inhibitors
- prednisone will require stress dose coverage, anticoagulation medication must be managed to decrease surgical bleeding but not put patient at risk for increased thrombotic events (e.g. switching from warfarin to LMWH)
- hold ASA x 1 wk pre-operative
- prophylactic antibiotics depending on wound class (within 1 h prior to incision): usually cefazolin (Ancef®) ± metronidazole (Flagyl®)
- consider bowel prep: cleans out bowel and decreases bacterial population
  - oral cathartic (e.g. fleet Phosphosoda®) starting previous day
  - in selected cases, current evidence does not support routine use
- consider DVT prophylaxis for all inpatient surgery (heparin)
- do not hold heparin prior to surgery unless epidural is expected
- smoking cessation x 8 or more wk and weight loss pre-operative can significantly decrease post-operative complications
- infection: delay elective surgery until infection controlled including respiratory infection particularly in asthma patients

**Investigations**

- see Anesthesia and Perioperative Medicine, A3
- routine pre-operative laboratory investigations for elective procedures should be selective
  - only ASA class and surgical risk have been found to independently predict post-operative adverse effects
- blood components: group and screen or cross and type depending on procedure
- CBC, electrolytes, BUN, creatinine
- INR/PT, PTT
- ABGs if predisposed to respiratory insufficiency
- ECG (PA and lateral) for patients with history of cardiac or pulmonary disease
- ECG as indicated by history or if >69 yr and no risk factors
- β-hCG testing in all women of reproductive age

**Biochemical Signs for Differentiating Jaundice**

- Hepatocellular: Elevated bilirubin + elevated ALT/AST
- Cholestatic: Elevated bilirubin + elevated ALP/GGT ± duct dilatation upon biliary U/S
- Hemolysis:↓ haptoglobin ↑ LDH

**Note:** cholestatic jaundice is usually surgical

**Bilirubin Levels**

<table>
<thead>
<tr>
<th>Type</th>
<th>Prehepatic</th>
<th>Intrahepatic</th>
<th>Posthepatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Bilirubin</td>
<td>↑</td>
<td>↑</td>
<td>N</td>
</tr>
<tr>
<td>Direct</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Urobilinogen</td>
<td>↑</td>
<td>↑</td>
<td>-</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fecal Urobilinogen</td>
<td>↑</td>
<td>↑</td>
<td>-</td>
</tr>
</tbody>
</table>

In patients with liver disease and an acute abdomen, spontaneous bacterial peritonitis must be ruled out

**Best Practice in General Surgery (BPIGS)**

http://www.bpigs.ca/

BPIGS is a University of Toronto initiative with the goal of standardizing care in general surgery. This link contains EBM based guidelines which have been implemented by consensus within all Toronto teaching hospitals. This is a highly recommended source for the most up-to-date pre-operative and general treatment guidelines

**Surgical Emergencies: Take an AMPLE History**

- Allergies
- Medications
- Past medical/surgical history (including anesthesia and bleeding disorders)
- Last meal
- Events (HPI and FHx of bleeding disorders/anesthesia complications)
Drains
• NGT
  • indications: gastric decompression, analysis of gastric contents, irrigation/dilution of gastric contents, feeding (only if necessary due to risk of aspiration → naso-jejunal tube preferable)
  • contraindications: suspected basal skull fracture, obstruction of nasal passages due to trauma
• Foley catheter with urometer
  • indications: to accurately monitor urine output, decompression of bladder, relieve obstruction, rapidly expanding suprapubic mass
  • contraindications: suspected urethral injury, difficult insertion of catheter

Surgical Complications

• general principles in preventing complications during the post-operative period include
  • frequent examination of the patient (daily or more) and their wound
  • removal of surgical tubes as soon as possible (e.g. Foley catheters and surgical drains)
  • early ambulation
  • monitor fluid balance and electrolytes
  • analgesia - enough to adequately address pain, but not excessive
  • skillful nursing care

Post-Operative Fever

• fever does not necessarily imply infection particularly in the first 24-48 h post-operative
• fever may not be present or is blunted if patient is receiving chemotherapy, glucocorticoids, or immunosuppression
• timing of fever may help identify cause
  • hours after surgery – POD #1 (immediate)
    • inflammatory reaction in response to trauma from surgery; unlikely to be infectious
    • reaction to blood products received during surgery
    • malignant hyperthermia
  • POD #1-2 (acute)
    • atelectasis (most common cause of fever on POD #1)
    • early wound infection (especially *Clostridium*, Group A *Streptococcus* – feel for crepitus and look for “dishwater” drainage)
    • aspiration pneumonitis
    • other: Addisonian crisis, thyroid storm, transfusion reaction
  • POD #3-7 (subacute): likely infectious
    • UTI, surgical site infection, IV site/line infection, septic thrombophlebitis, leakage at bowel anastomosis (tachycardia, hypotension, oliguria, abdominal pain)
  • POD #8+ (delayed)
    • intra-abdominal abscess, DVT/PE (can be anytime post-operative, most commonly POD #8-10), drug fever
    • other: cholecystitis, peri-rectal abscess, URTI, infected seroma/biloma/hematoma, parotitis, *C. difficile* colitis, endocarditis

Treatment
• treat primary cause
• antipyrexia (e.g. acetaminophen)

Wound/Incisional Complications

WOUND CARE (see Plastic Surgery, PL8)
• can shower POD #2-3 after epithelialization of wound
• dressings can be removed POD #2 and left uncovered if dry
• examine wound if wet dressing, signs of infection (fever, tachycardia, pain)
• skin sutures and staples can be removed POD #7-10
  • exceptions: incision crosses crease (groin), closed under tension, in extremities (hand) or patient factors (elderly, corticosteroid use, immunosuppressed) removed POD #14, earlier if signs of infection
• negative pressure dressings consist of foam and suction, promote granulation
  • ideal for large (grafted sites) or non-healing wounds (irradiated skin, ulcer)

DRAINS
• sometimes placed intra-operatively to prevent fluid accumulation (blood, pus, serum, bile, urine)
  • can be used to assess quantity of third space fluid accumulation post-operatively
• potential route of infection, bring out through separate incision (vs. operative wound) to decrease risk of wound infection and remove as soon as possible

Drain Size
Measured by the unit French:
French = diameter (mm) x 3
• **types of drains**
  - open (e.g. Penrose), higher risk of infection
  - closed: 1) Gravity drainage (e.g. Foley catheter); 2) Underwater-seal drainage system (e.g. chest tube); 3) Suction drainage (e.g. Jackson-Pratt)
  - sump (e.g. NGT)

• monitor drain outputs daily

• drains should be removed once drainage is minimal (usually <30-50 cc/24 h)

• evidence does not support routine post-operative drainage of abdominal cavity

• drains do not guarantee that the patient will not form a collection of fluid

• ridged drains can erode through internal structures, and excessive suction can cause necrosis

### SURGICAL SITE INFECTION

#### Etiology

- *S. aureus*, *E. coli*, *Enterococcus*, *Streptococcus* spp., *Clostridium* spp.

#### Risk Factors

**Table 4. Procedures and Their Impact on Surgical Site Infection**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clean</th>
<th>Clean-Contaminated</th>
<th>Contaminated</th>
<th>Dirty/Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Incision under sterile</td>
<td>Incision under</td>
<td>Incision under sterile</td>
<td>Established infection</td>
</tr>
<tr>
<td></td>
<td>conditions; nontraumatic;</td>
<td>sterile conditions;</td>
<td>sterile conditions;</td>
<td>present before wound</td>
</tr>
<tr>
<td></td>
<td>no entrance of hollow</td>
<td>ENTRANCE of hollow</td>
<td>MAJOR contamination of</td>
<td>is made in skin</td>
</tr>
<tr>
<td></td>
<td>organ</td>
<td>viscus; no</td>
<td>wound during procedure (i.e.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>evidence of active</td>
<td>gross spillage of stool,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>infection; minimal</td>
<td>infection in biliary,</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>contamination</td>
<td>respiratory, or GU systems)</td>
<td></td>
</tr>
<tr>
<td><strong>Example</strong></td>
<td>Wound created to repair</td>
<td>Routine cholecystectomy;</td>
<td>Bowel obstruction with</td>
<td>Appendiceal abscess;</td>
</tr>
<tr>
<td></td>
<td>hemia</td>
<td>colon resection</td>
<td>enterotomy and spillage of</td>
<td>traumatic wound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>contents; necrotic bowel</td>
<td>with contaminated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>resection; fresh traumatic</td>
<td>devitalized tissue;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>wounds</td>
<td>perforated viscus</td>
</tr>
<tr>
<td><strong>Infection Rate</strong></td>
<td>&lt;2%</td>
<td>3-4%</td>
<td>7-10%</td>
<td>30-40%</td>
</tr>
<tr>
<td><strong>Wound Closure</strong></td>
<td>Primary closure</td>
<td>Primary closure</td>
<td>Often secondary closure</td>
<td>Secondary closure</td>
</tr>
</tbody>
</table>

- patient characteristics
  - age, DM, steroids, immunosuppression, obesity, burn, malnutrition, patient with other infections, traumatic wound, radiation, chemotherapy
- other factors
  - prolonged pre-operative hospitalization, reduced blood flow, break in sterile technique, multiple antibiotics, hematoma, seroma, foreign bodies (drains, sutures, grafts), skin preparation, hypoxemia, hypothermia

#### Clinical Presentation

- typically fever POD #5-8 (*Streptococcus* and *Clostridium* can present in 24 h)
- pain, blanchable wound erythema, induration, purulent discharge, warmth
- complications: fistula, sinus tracts, sepsis, abscess, suppressed wound healing, superinfection, spreading infection to myonecrosis or fascial necrosis (necrotizing fasciitis), wound dehiscence, evisceration, hernia

#### Prophylaxis

- used to reduce the chance of surgical site infections
- pre-operative antibiotics for most surgeries (cefazolin ± metronidazole or if β-lactam allergy, clindamycin ± gentamycin)
  - within 1 h pre-incision; can re-dose at 1-2 half-lives (~q4-8h) in the OR
  - not required for low risk elective cholecystectomy, hemorrhoidectomy, fistulotomy, sphincterotomy for fissure
  - evidence suggests role in breast surgery
- generally no need to continue prophylactic antibiotics post-operatively
  - reserve post-operative antibiotics for treatment of suspected or documented intra-abdominal infection
- normothermia (maintain patient temperature 36-38°C during OR)
- hyperoxygenation (consider FiO₂ of 80% in OR)
- chlorhexidine-alcohol wash of surgical site
- hair removal should not be performed unless necessary; if so, clipping superior to shaving
- consider delayed primary closure of incision for contaminated wounds

#### Systemic Prophylactic Antibiotics Recommendations

Updated Recommendations for Control of Surgical Site Infections

*Ann Surg* 2011;253:1082-93

- Choice of routine prophylactic antibiotic depends on the pathogen and patient allergies.
- Vancomycin and fluoroquinolones should be administered 1-2 h prior to incision; all other antibiotics should be administered 30 min prior to incision.
- Short-acting antibiotics should be redosed ~3 h after incision.
- Antibiotic administration >24 h after surgery does not appear to add benefits.
- Antibiotics should no longer be routinely administered in three doses.
- The majority of antibiotics are renally excreted hence renal function must be considered in antibiotic administration.
- Obese patients need higher antibiotic doses to achieve therapeutic concentrations.
- Drug half-life and length of operation need to be considered in antibiotic administration.
Treatment
• examination of the wound: inspect, compress adjacent areas, swab drainage for C&S and Gram stain
• re-open affected part of incision, drain, pack, heal by secondary intention in most cases
• for deeper infections, debride necrotic and non-viable tissue
• antibiotics and demarcation of erythema only if cellulitis or immunodeficiency

WOUND HEMORRHAGE/HEMATOMA
• secondary to inadequate surgical control of hemostasis

Risk Factors
• anticoagulant therapy, coagulopathies, thrombocytopenia, DIC, severe liver disease, myeloproliferative disorders, severe arterial HTN, severe cough
• more common with transverse incisions through muscle, due to cutting of muscle

Clinical Features
• pain, swelling, discoloration of wound edges, leakage
• rapidly expanding neck hematoma can compromise airway and is a surgical emergency: consider having a suture kit at bedside in all neck surgery in the event of having to open the wound emergently

Treatment
• pressure dressing
• open drainage ± wound packing (large hematoma only)
• if significant bleeding, may need to re-operate to find source (often do not find a discrete vessel)

SEROMA
• fluid collection other than pus or blood
• secondary to transection of lymph vessels
• delays healing
• increased infection risk

Treatment
• consider pressure dressing ± needle drainage
• if significant may need to re-operate

WOUND DEHISCENCE
• disruption of fascial layer, abdominal contents contained by skin only
• 95% caused by intact suture tearing through fascia

Clinical Features
• typically POD #1-3; most common presentation sign is serosanguinous drainage from wound ± evisceration
• palpation of wound edge: should normally feel a “healing ridge” from abdominal wall closure (raised area of tissue under incision)

Risk Factors
• local: technical failure of closure, increased intra-abdominal pressure (e.g. COPD, ileus, bowel obstruction), hematoma, infection, poor blood supply, radiation, patient not fully paralyzed while closing, transverse incision
• systemic: smoking, malnutrition (hypoalbuminemia, vitamin C deficiency), connective tissue diseases, immunosuppression, pulmonary disease, ascites, poor nutrition, steroids, chemotherapy, obesity, other (e.g. age, sepsis, uremia)
• DM alone is not a risk factor

Treatment
• place moist dressing over wound with binder around abdomen and transfer to OR
• may consider conservative management with debridement of fascial and/or skin margins
• evisceration, also known as ‘burst abdomen’, is a surgical emergency (mortality rates as high as 45%): take patient for operative closure, use slowly absorbable suture ± retention sutures
Urinary and Renal Complications

URINARY RETENTION
• may occur after any operation with general anesthesia or spinal anesthesia
• more likely in older males with history of benign prostatic hyperplasia, patients on anticholinergics

Clinical Presentation
• abdominal discomfort, palpable bladder, overflow incontinence, post-void residual urine volume >100 mL

Treatment
• Foley catheter to rest bladder, then trial of voiding

OLIGURIA/ANURIA (see Nephrology, NP17)

Etiology
• prerenal vs. renal vs. postrenal
  • most common post-operative cause is prerenal ± ischemic ATN
  • external fluid loss: hemorrhage, dehydration, diarrhea
  • internal fluid loss: third-spacing due to bowel obstruction, pancreatitis

Clinical Presentation
• urine output <0.5 cc/kg/h, increasing Cr, increasing BUN

Treatment
• according to underlying cause; fluid deficit is treated with crystalloid (NS or RL)

Post-Operative Dyspnea

• see Respiratory Complications below and Cardiac Complications, GS11

Etiology
• respiratory: atelectasis, pneumonia, pulmonary embolus (PE), ARDS, asthma, pleural effusion
• cardiac: MI, arrhythmia, CHF
• inadequate pain control

Respiratory Complications

ATELECTASIS
• comprises 90% of post-operative pulmonary complications

Clinical Features
• low-grade fever on POD #1, tachycardia, crackles, decreased breath sounds, bronchial breathing, tachypnea

Risk Factors
• COPD, smoking, obesity, elderly persons
• upper abdominal/thoracic surgery, oversedation, significant post-operative pain, poor inspiratory effort

Treatment
• pre-operative prophylaxis
  • smoking cessation (best if >8 wk pre-operative)
• post-operative prophylaxis
  • incentive spirometry, deep breathing exercise, chest physiotherapy, intermittent positive-pressure breathing
  • selective NGT decompression after abdominal surgery
  • short-acting neuromuscular blocking agents
  • minimize use of respiratory depressive drug, good pain control, early ambulation

PNEUMONIA/PNEUMONITIS
• may be secondary to aspiration of gastric contents during anesthetic induction or extubation, causing a chemical pneumonitis

Risk Factors
• aspiration: general anesthetic, decreased LOC, GERD, full stomach, bowel/gastric outlet obstruction + non-functioning NGT, pregnancy, seizure disorder
• non-aspiration: atelectasis, immobility, pre-existing respiratory disease
Clinical Features
- productive cough, fever
- tachycardia, cyanosis, respiratory failure, decreased LOC
- CXR: pulmonary infiltrate

Treatment
- prophylaxis: see atelectasis prophylaxis, pre-operative NPO/NGT, rapid sequence anesthetic induction
- immediate removal of debris and fluid from airway
- consider endotracheal intubation and flexible bronchoscopic aspiration
- IV antibiotics to cover oral nosocomial aerobes and anaerobes (e.g. ceftiraxone, metronidazole)

PULMONARY EMBOLUS (see Respirology, R18)

Clinical Features
- unilateral leg swelling and pain (DVT as a source of PE), sudden onset shortness of breath, tachycardia, fever
- most commonly POD #8-10, but can occur anytime post-operatively
- diagnosis made by Chest CT scan usually

Treatment
- IV heparin, long-term warfarin (INR = 2-3) for 3 mo
- Greenfield (IVC) filter if contraindications to anticoagulation
- prophylaxis: subcutaneous heparin (5,000 U bid) or LMWH, compression stockings (TED’ Hose)

PULMONARY EDEMA

Etiology
- cardiogenic vs. noncardiogenic
- circulatory overload: excess volume replacement, LV failure, shift of fluid from peripheral to pulmonary vascular bed, negative airway pressure, alveolar injury due to toxins (e.g. ARDS)
  - more common with pre-existing cardiac disease
- negative pressure pulmonary edema due to inspiratory efforts against a closed glottis upon awakening from general anesthesia

Clinical Features
- shortness of breath, crackles at lung bases, CXR abnormal

Treatment (LMNOP)
- Lasix
- Morphine (decreases symptoms of dyspnea, venodilator and afterload reduction)
- Nitrates (venodilator)
- Oxygen + non-invasive ventilation
- Position (sit patient up)

RESPIRATORY FAILURE

Clinical Features
- dyspnea, cyanosis, evidence of obstructive lung disease
- earliest manifestations – tachypnea and hypoxemia (RR >25, pO2 <60)
- pulmonary edema, unexplained decrease in SaO2

Treatment
- ABCs, O2, ± intubation
- bronchodilators, diuretics to treat CHF
- adequate blood pressure to maintain pulmonary perfusion
- if these measures fail to keep PaO2 >60, consider ARDS

New onset “asthma” and wheezing in the elderly is cardiogenic until proven otherwise
Cardiac Complications

- abnormal ECGs common in post-operative period (compare to pre-operative ECG)
- common arrhythmias: supraventricular tachycardia, atrial fibrillation (secondary to fluid overload, PE, MI)

Myocardial Infarction

- see Cardiology and Cardiac Surgery, C26
- surgery increases risk of MI
- incidence
  - 0.5% in previously asymptomatic men >50 yr old
  - 40-fold increase in men >50 yr old with previous MI

Risk Factors

- pre-operative HTN, CHF
- previous MI (highest risk ≤6 mo, but risk never returns to baseline)
- increased age
- intra-operative hypotension
- operations >3 h
- angina

Clinical Features

- majority of cases on day of operation or POD #3-4 (shifting of third space fluid back into intravascular compartment)
- often silent without chest pain, may only present with new-onset CHF (dyspnea), arrhythmias, hypotension

Intra-Abdominal Abscess

Definition

- collection of pus walled-off from rest of peritoneal cavity by inflammatory adhesions and viscera

Etiology

- usually polymicrobial: Gram-negative bacteria, anaerobes
  - consider Gram-positives if coexisting cellulitis

Risk Factors

- emergency, contaminated OR
- GI surgery with anastomoses
- poor healing risk factors (DM, poor nutrition, etc.)
- may occur POD #3 after laparotomy when third space fluid re-distribution occurs

Clinical Features

- persistent spiking fever, dull pain, weight loss
- mass difficult to palpate
- peritoneal signs if abscess perforation and secondary peritonitis
- leukocytosis or leukopenia (immunocompromised, elderly)
- co-existing effusion (pleural effusion with subphrenic abscess)
- common sites: pelvis, Morrison's pouch (space between kidney and liver), subphrenic, paracolic gutters, lesser sac, peri-appendiceal, post-surgical anastomosis, diverticular, psoas

Investigations

- CBC, blood cultures x2
- CT ± water-soluble contrast
- DRE (pelvic abscess)

Treatment

- drain placement by interventional radiology (preferred), laparoscopy, open drainage
- subsequent antibiotic coverage, ciprofloxacin (Cipro®) + metronidazole (Flagyl®)

Paralytic Ileus

- see Bowel Obstruction, GS24

Delirium

- see Psychiatry, PS20 and Neurology, N21
SLIDING HIATUS HERNIA (Type I)
- see Figure 6
- herniation of both the stomach and the gastroesophageal (GE) junction into thorax
- 90% of esophageal hernias

Risk Factors
- age
- increased intra-abdominal pressure (e.g. obesity, pregnancy, coughing, heavy lifting)
- smoking

Clinical Features
- majority are asymptomatic
- larger hernias frequently associated with GERD due to decreased competence of LES

Complications
- most common complication is GERD
- other complications are rare and are related to reflux
  - esophagitis (dysphagia, heartburn)
  - consequences of esophagitis (peptic stricture, Barrett’s esophagus, esophageal carcinoma)
  - extra-esophageal complications (pneumonitis/pneumonia, asthma, cough, laryngitis)

Investigations
- CXR, barium swallow, endoscopy, or esophageal manometry (technique for measuring LES pressure)
- 24 h esophageal pH monitoring to quantify reflux
- gastroscopy with biopsy to document type and extent of tissue damage and rule out esophagitis, Barrett’s esophagus, and cancer

Treatment
- lifestyle modification
  - stop smoking, weight loss, elevate head of bed, no meals <3 h prior to sleeping, smaller and more frequent meals, avoid alcohol, coffee, mint, and fat
- medical
  - antacid, H₂-antagonist, PPI, prokinetic agent
- surgical (<15%)
  - if failure of medical therapy, esophageal stricture, severe nocturnal aspiration, Barrett’s esophagus
  - anti-reflux procedure (usually laparoscopic) e.g. Nissen fundoplication
    - fundus of stomach is wrapped around the lower esophagus and sutured in place
    - 90% success rate
**PARAESOPHAGEAL HIATUS HERNIA (Type II)**
- see Figure 6
- herniation of all or part of the stomach through the esophageal hiatus into the thorax with an undisplaced GE junction
- least common esophageal hernia (<10%)

**Clinical Features**
- usually asymptomatic due to normal GE junction
- pressure sensation in lower chest, dysphagia

**Complications**
- hemorrhage, incarceration, strangulation (gastric volvulus), obstruction, gastric stasis ulcer (Cameron’s lesion – causes Fe-deficiency anemia)

**Treatment**
- surgery to prevent severe complications
  - reduce hernia and excise hernia sac, repair defect at hiatus, and anti-reflux procedure (e.g. Nissen fundoplication)
  - may consider suturing stomach to anterior abdominal wall (gastropexy)
  - in very elderly patients at high surgical risk consider PEG (percutaneous endoscopic gastrostomy)

**MIXED HIATUS HERNIA (Type III)**
- see Figure 6
- combination of Types I and II

**TYPE IV HERNIA**
- herniation of other abdominal organs into thorax: colon, spleen, small bowel

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**Esophageal Perforation**

**Etiology**
- iatrogenic (most common)
  - endoscopic, dilatation, biopsy, intubation, operative, NGT placement
- barogenic
  - trauma
  - repeated, forceful vomiting (Boerhaave’s syndrome)
  - other: convulsions, defecation, labour (rare)
- ingestion injury
  - foreign body, corrosive substance
- carcinoma

**Clinical Features**
- neck or chest pain
- fever, tachycardia, hypotension, dyspnea, respiratory compromise
- subcutaneous emphysema, pneumothorax, hematemesis

**Investigations**
- CXR: pneumothorax, pneumomediastinum, pleural effusion, subdiaphragmatic air
- CT chest: widened mediastinum, pneumomediastinum
- contrast swallow (water-soluble then thin barium): contrast extravasation

**Treatment**
- supportive if rupture is contained
  - NPO, vigorous fluid resuscitation, broad-spectrum antibiotics, possible percutaneous drainage
- surgical
  - <24 h
    - primary closure of a healthy esophagus or resection of diseased esophagus
  - >24 h or non-viable wound edges
    - diversion and exclusion followed by delayed reconstruction (i.e. esophagostomy proximally, close esophagus distally, gastrostomy/jejunalostomy for decompression/feeding)

**Complications**
- sepsis, abscess, fistula, empyema, mediastinitis, death
- post-operative esophageal leak
- mortality 10-50% dependent on timing of diagnosis
Esophageal Carcinoma

Epidemiology
- M:F = 3:1
- onset 50-60 yr of age
- upper (20-33%), middle (33%), lower (33-50%)
- main types:
  - most common worldwide: SCC in upper 2/3 of esophagus
  - most common in Western countries: adenocarcinoma in distal 1/3 of esophagus

Risk Factors
- geographic variation in incidence
- SCC
  - underlying esophageal disease such as strictures, diverticula, achalasia
  - smoking, alcohol, hot liquids
  - more common in patients from Asia
- adenocarcinoma
  - Barrett’s esophagus (most important), smoking, obesity (increased reflux), GERD

Clinical Features
- frequently asymptomatic: late presentation
- progressive dysphagia (mechanical): first solids then liquids
- odynophagia then constant pain
- constitutional symptoms
- regurgitation and aspiration (aspiration pneumonia)
- hematemesis, anemia
- tracheoesophageal or bronchoesophageal fistula
- direct, hemogenous, or lymphatic spread
  - trachea (coughing), recurrent laryngeal nerves (hoarseness, vocal paralysis), aortic, liver, lung, bone, celiac and mediastinal nodes

Investigations and Staging
- barium swallow: shows narrowing – suggestive but not diagnostic
- esophagoscopy: biopsy and assess resectability
- both SCC and adenocarcinoma use TNM staging system but have separate stage groupings according to histology
- endoscopic U/S (EUS)
  - visualize local disease
  - regional nodal involvement (number of nodes may be more important than location)
- bronchoscopy ± thoracoscopy
  - rule out airway invasion in tumours of the upper and mid esophagus
- full metastatic workup (CXR, bone scan, CT head, CT chest/abdomen/pelvis, LFTs, etc.)
- PET scan more sensitive than CT in detecting metastatic disease

Treatment
- if present with distant metastatic disease
  - treat with systemic therapy and treat symptoms (esophageal stent)
- if locally advanced (locally invasive disease or nodal disease on CT or EUS)
  - multimodal therapy
    - concurrent external beam radiation and chemotherapy (cisplatin and 5-FU)
    - possibility of curative esophagectomy after chemoradiation if disease responds well
  - if unable to tolerate multimodal therapy or if highly advanced disease, consider palliative resection, brachytherapy, or endoscopic dilatation/stenting/laser ablation for palliation
- if early stage (non-transmural and without evidence of nodal disease)
  - esophagectomy (transthoracic or trans-hiatal approach) and lymphadenectomy
  - anastomosis in chest or neck
  - stomach most often used for reconstruction; may also use colon
  - neoadjuvant chemotherapy and radiation are controversial
- adjuvant chemotherapy ± radiation usually recommended for post-operative node-positive disease

Prognosis
- prognosis usually poor because presentation is usually at advanced stage

OTHER DISORDERS
- esophageal motor disorders (see Gastroenterology, G8)
- esophageal varices (see Gastroenterology, G26)
- Mallory-Weiss tear (see Gastroenterology, G26)
**Thymoma**

**Epidemiology**
- most common neoplasms in thymus including both thymoma and thymic carcinoma
- patients between 40 and 60 yr
- M > F

**Risk Factors**
- no known risk factors, strong association with myasthenia gravis and other paraneoplastic syndromes

**Clinical presentation**
- frequently asymptomatic: incidental finding on imaging
- symptoms related to tumour size and location: chest pain, SOB, cough, phrenic nerve palsy
- ddx includes lymphoma, other anterior mediastinal tumours (see Respiratory, R21)

**Investigations**
- CT chest (and/or MRI)
- Germ cell tumor markers (β-hcg, alpha fetoprotein), thyroid function, PFTs

**Treatment**
- for patients with resectable disease
- open surgical resection of thymus via median sternotomy
- ± post-operative radiation based on Masaoka staging
- for non-surgical patients
- multimodal therapy including neoadjuvant or palliative chemotherapy and post-operative chemoradiotherapy if de-bulking procedure feasible

**Prognosis**
- depends upon stage of disease and resectability
- generally slow growing tumours

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**Pleura, Lung, and Mediastinum**

- see Respiratory, R22

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**Tube Thoracostomy**

**Indications**
- to drain abnormal large-volume air or fluid collections in the pleural space
  - hemothorax, chylothorax, empyema
  - pneumothorax, if
    - large or progressive
    - patient is on mechanical ventilation
    - bronchopleural fistula
    - tension pneumothorax
- to treat symptomatic and/or recurrent pleural effusion
  - see Respiratory, R22
  - for long-term drainage of malignant effusions
  - via facilitation of pleurodesis (obliteration of the pleural space by instilling talc or doxycycline to cause fibrosis and adherence of parietal and visceral pleura)

**Complications**
- overall complications are rare (1-3%)
- malposition (most common complication), especially by inexperienced operators
  - tubes may dissect along the external chest wall, or may be placed below the diaphragm
- bleeding (anticoagulation is a relative contraindication)
- local infection, empyema
- perforation of lung parenchyma
- risk of re-expansion pulmonary edema when large volumes of air or fluid are drawn off quickly (>1.0-1.5 L)
Lung Transplantation

Conditions Leading to Transplantation
- chronic acquired lung disease: COPD
- genetic: CF, emphysema due to α-1 antitrypsin deficiency
- idiopathic interstitial pneumonias: IPF, nonspecific interstitial pneumonitis
- HTN-related: IPAH, secondary pulmonary HTN, Eisenmenger’s syndrome
- other: sarcoidosis, lymphangioleiomyomatosis, pulmonary Langerhans cell histiocytosis

Clinical Indications
- transplantation should be considered for patients with advanced lung disease refractory to maximal medical or surgical therapy
- patients who are symptomatic during activities of daily living and limited expected survival over the next 2 yr

Criteria for Transplantation
- lung allocation score based on: 1) post-transplant survival measure, and 2) waiting list urgency measure
- transplant benefit = post-transplant survival (days) – waitlist survival (days)

Contraindications
- uncontrolled or untreatable pulmonary or extrapulmonary infection
- malignancy in the last 2 yr
- advanced cardiopulmonary disease
- significant chest wall/spinal deformity
- active cigarette smoking
- HIV infection, ongoing HBV or HCV infections

Post-Operative Complications
- primary graft dysfunction: main cause is ischemia-reperfusion injury, graded by PaO₂/FiO₂ ratio and CXR findings
- airway anastomotic complications (focal infection, bronchial necrosis and dehiscence, excess granulation tissue, tracheobronchomalacia, stenosis, fistula)
- chronic graft dysfunction: bronchiolitis obliterans syndrome
- infectious complications (bacterial, fungal, CMV, community-acquired respiratory viruses, mycobacteria)
- malignancy (non-melanoma skin cancer, post-transplant lymphoproliferative disease, colon, breast, Kaposi’s sarcoma, bladder)

Prognosis
- median survival for all adult recipients: 5.4 yr
- 1 yr survival: COPD > IPF > IPAH
- 10 yr survival: CF, α-1 antitrypsin deficiency > IPAH > COPD, IPF

Chronic Obstructive Pulmonary Disease
- see Respirology, R9

Treatment
- indications for surgical management
  - dyspnea despite maximal medical therapy and pulmonary rehabilitation
  - CT showing hyperinflation and heterogeneously distributed emphysema predominant in the upper lung zone
  - may be used as a bridging procedure to lung transplantation
- contraindications
  - age >75, cigarette smoking within the prior 6 mo, higher risk of surgical mortality
  - homogeneously distributed emphysematous changes without areas of preserved lung tissue
  - diffusing capacity of lung for carbon monoxide <20% of predicted, PaCO₂ >60 mmHg, PaO₂ <45 mmHg
- surgical procedures
  - lung volume reduction surgery: wedge excision of emphysematous tissue
  - bilateral or unilateral, thoracotomy or VATS

Complications of Treatment
- air leak: may require reintubation and mechanical ventilation
- arrhythmias, pneumonia

Prognosis
- total mortality at 2 yr same as with maximal medical therapy, but better exercise capacity and quality of life with LVRS

Long-Term Survival Analysis of the Canadian Lung Volume Reduction Surgery Trial
Study: Retrospective observational study assessing the long-term survival of patients enrolled in the CLVRS at 8-10 yr follow-up.
Results/Conclusions: 62 patients total. 52 patients had a median survival time of 4.11 yr. Compared with the best medical care group, patients in the LVRS group showed a 16-mo survival advantage and a 20% reduction in mortality. LVRS may provide long-term benefits in the treatment of end-stage emphysema, however, the results were not statistically significant.
**Peptic Ulcer Disease**

**GASTRIC ULCERS**
- see *Gastroenterology, G12*

**Indications for Surgery**
- refractory to medical management (intractability)
- suspicion of malignancy even if biopsy benign
- complications of PUD: obstruction, perforation, bleeding (3x greater risk compared to duodenal ulcers)
- surgical treatment is increasingly rare due to *H. pylori* eradication and medical treatment

**Procedures**
- ligation of bleeding vessels
- distal gastrectomy with ulcer excision: Billroth I or Billroth II or Roux-en-Y
- vagotomy and pyloroplasty only if acid hypersecretion (rare)
- wedge resection if possible or biopsy with primary repair

**DUODENAL ULCERS**
- see *Gastroenterology, Bleeding Peptic Ulcer, G12, and Peptic Ulcer Disease, G12*
- most within 2 cm of pylorus (duodenal bulb)

**Indications for Surgery**
- hemorrhage, rebleed in hospital, perforation, gastric outlet obstruction
- refractory to medical management (endoscopy)

**Procedures**
- Graham patch of perforated ulcer—plication of ulcer and omental patch
- oversewing of bleeding ulcer ± pyloroplasty
- pyloroplasty, gastrojejunostomy, or gastrojejunostomy (improved drainage)
- antrrectomy (eliminate hormonal stimulation from the antrum)
- gastric resection (decrease the number of parietal cells)
- vagotomy
  - rarely done now due to *H. pylori* eradication and PPI

**Complications of Surgery**
- retained antrum
- fistula (gastrocolic/gastrojejunal)
- dumping syndrome, postvagotomy diarrhea, af ferent loop syndrome (see *Complications of Gastric Surgery, GS20*)

**Table 5. Complications of Duodenal Ulceration**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Clinical Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perforated Ulcer (typically on anterior surface)</td>
<td>Sudden onset of pain (possibly in RLQ due to track down right paracolic gutter), Acute abdomen: rigid, diffuse guarding ileus, Initial chemical peritonitis followed by bacterial peritonitis</td>
<td>Investigation, CXR – free air under diaphragm (70% of patients), Treatment: oversew ulcer (plication) and omental (Graham) patch – most common treatment</td>
</tr>
<tr>
<td>Posterior Penetration</td>
<td>Elevated amylase/lipase if penetration into pancreas, Constant mid-epigastric pain burrowing into back, unrelated to meals</td>
<td>Resuscitation initially with crystalloids; blood transfusion if necessary, Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope, Consider interventional radiology: angiography with embolization/coiling, Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty</td>
</tr>
<tr>
<td>Hemorrhage (typically on posterior surface)</td>
<td>Gastroduodenal artery involvement</td>
<td>Resuscitation initially with crystalloids; blood transfusion if necessary, Diagnostic and/or therapeutic endoscopy (laser, cautery, or injection); if recurs, may have second scope, Consider interventional radiology: angiography with embolization/coiling, Surgery if severe or recurrent bleeding, hemodynamically unstable, or failure of endoscopy and IR: oversewing of ulcer, pyloroplasty</td>
</tr>
</tbody>
</table>
### Table 5. Complications of Duodenal Ulceration (continued)

<table>
<thead>
<tr>
<th>Complication</th>
<th>Clinical Features</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric Outlet Obstruction</td>
<td>Ulcer can lead to edema, fibrosis of pyloric channel, neoplasm</td>
<td>NGT decompression and correction of hypochloremic, hypokalemic metabolic alkalosis</td>
</tr>
<tr>
<td></td>
<td>N/V (undigested food, non-bilious), dilated stomach, crampy abdominal pain</td>
<td>Medical management initially: high dose PPI therapy</td>
</tr>
<tr>
<td></td>
<td>Succussion splash (splashing noise heard with stethoscope over the stomach when patient is shaken)</td>
<td>Surgical resection if obstruction does not resolve: either Billroth I, pyloroplasty, or gastrojejunostomy</td>
</tr>
<tr>
<td></td>
<td>Auscultate gas and fluid movement in obstructed organ</td>
<td></td>
</tr>
</tbody>
</table>

### Gastric Carcinoma

#### Epidemiology
- 9th most common cancer in the world
- M:F = 3:2
- incidence of adenocarcinoma <10 (US) vs. 40 (Japan, Korea) per 100,000 (incidence highest in Asia, Latin America, and Caribbean)
- most common age group = 50-59 yr
- incidence has decreased by 2/3 in past 50 yr

#### Risk Factors
- compensatory epithelial cell proliferation via gastric atrophy from:
  - *H. pylori*, causing chronic atrophic gastritis
  - pernicious anemia associated with achlorhydria and chronic atrophic gastritis
  - previous partial gastrectomy (>10 yr post-gastrectomy)
- host-related factors
  - blood type A
  - hereditary nonpolyposis colorectal cancer (HNPPC), hereditary diffuse gastric carcinoma (HDGC)
  - gastric adenomatous polyps
  - hypertrophic gastropathy
- environmental factors: smoking, alcohol, smoked food, nitrosamines

#### Clinical Features
- clinical suspicion
  - ulcer fails to heal
  - lesion on greater curvature of stomach or cardia
- asymptomatic, insidious, or late onset of symptoms
  - postprandial abdominal fullness, vague epigastric pain
  - anorexia, weight loss
  - burping, N/V, dyspepsia, dysphagia
  - hepatomegaly, epigastric mass (25%)
  - hematemesis, fecal occult blood, melena, iron-deficiency anemia
- metastasis
  - peritoneum, liver, lung, brain

#### Investigations
- OGD and biopsy; EUS to assess pre-operative T-stage and N-stage
- CT chest/abdomen/pelvis (for metastatic workup see Table 7)

#### Table 6. TNM Classification System for Staging of Gastric Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>NX</td>
<td>Cannot be assessed</td>
</tr>
<tr>
<td>Tis</td>
<td>N0</td>
<td>No regional node</td>
</tr>
<tr>
<td>T1a</td>
<td>N1</td>
<td>Metastasis in 1-2 regional nodes</td>
</tr>
<tr>
<td>T1b</td>
<td>N2</td>
<td>Metastasis in 3-6 regional nodes</td>
</tr>
<tr>
<td>T2</td>
<td>N3a</td>
<td>Metastasis in 7-15 regional nodes</td>
</tr>
<tr>
<td>T3</td>
<td>N3b</td>
<td>Metastasis in ≥16 regional nodes</td>
</tr>
<tr>
<td>T4a</td>
<td></td>
<td>M0</td>
</tr>
<tr>
<td>T4b</td>
<td></td>
<td>M1</td>
</tr>
</tbody>
</table>

#### Staging and 5 Yr Survival Rates for Gastric Cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>TNM</th>
<th>5-Yr Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1N0M0</td>
<td>71%</td>
</tr>
<tr>
<td>IB</td>
<td>T2N0M0</td>
<td>57%</td>
</tr>
<tr>
<td>IIA</td>
<td>T3N0M0</td>
<td>45%</td>
</tr>
<tr>
<td>IIB</td>
<td>T4aN0M0</td>
<td>33%</td>
</tr>
<tr>
<td>IIIA</td>
<td>T4aN1M0</td>
<td>20%</td>
</tr>
<tr>
<td>IIIB</td>
<td>T4aN2M0</td>
<td>14%</td>
</tr>
<tr>
<td>IIC</td>
<td>T4bN0M0</td>
<td>9%</td>
</tr>
<tr>
<td>IV</td>
<td>TxNxM1</td>
<td>4%</td>
</tr>
</tbody>
</table>

#### Signs of Metastatic Gastric Carcinoma
- Virchow’s node: left supraclavicular node
- Blumer’s shelf: mass in pouch of Douglas
- Krukenberg tumour: metastases to ovary
- Sister Mary Joseph node: umbilical metastases
- Irish’s node: left axillary nodes
Treatment
- adenocarcinoma
  - proximal lesions
    - total gastrectomy and Roux-en-Y esophagojejunostomy
  - distal lesions
    - distal gastrectomy: wide margins, en bloc removal of omentum and lymph nodes
- palliation
  - gastric resection to decrease bleeding and relieve obstruction, enables the patient to eat
  - radiation therapy
  - studies are showing larger role for chemotherapy
- lymphoma
  - *H. pylori* eradication, chemotherapy ± radiation, surgery in limited cases (perforation, bleeding, obstruction)

Gastrointestinal Stromal Tumour

Epidemiology
- most common mesenchymal neoplasm of GI tract
- derived from interstitial cells of Cajal (cells associated with Auerbach’s plexus that have autonomous pacemaker function which coordinate peristalsis throughout the GI tract)
- 75-80% associated with tyrosine kinase (c-KIT) mutations
- most common in stomach (50%) and proximal small intestine (25%), but can occur anywhere along GI tract
- typically present with vague abdominal mass, feeling of abdominal fullness, or with secondary symptoms of bleeding and anemia
- often discovered incidentally on CT, laparotomy, or endoscopy

Risk Factors
- Carney’s triad: GISTs, paraganglioma, and pulmonary chondroma
- Type IA neurofibromatosis

Investigations
- pre-operative biopsy: controversial, but useful for indeterminate lesions
  - not recommended if index of suspicion for GIST is high
  - percutaneous biopsy is NOT recommended due to high friability and risk of peritoneal spread

Treatment
- surgical resection if >2 cm; follow with serial endoscopy if <2 cm and resect if growing or symptomatic
- localized GIST
  - surgical resection with preservation of intact pseudocapsule
  - lymphadenectomy NOT recommended, as GISTs rarely metastasize to lymph nodes
  - consider imatinib post-operative for high-risk GIST (large, >4 cm with significant mitotic activity)
- advanced disease (i.e. metastases to liver and/or peritoneal cavity)
  - chemotherapy with imatinib

Prognosis
- risk of metastatic potential depends on
  - tumour size (worse if >10 cm)
  - mitotic activity (worse if >5 mitotic figures or 50/hpf)
  - degree of nuclear pleomorphism
  - location: with identical sizes, extra-gastric location has a higher risk of progression than GISTs in the stomach
- metastases to liver, omentum, peritoneum; nodal metastases rare

Bariatric Surgery
- weight reduction surgery for morbid obesity
- indications: BMI ≥40 without illness or BMI ≥35 with 1+ serious comorbidity (e.g. DM, CAD, sleep apnea, severe joint disease)

Surgical Options
- malabsorptive/restrictive
  - laparoscopic Roux-en-Y gastric bypass (most common – see Figure 9)
• staple off small gastric pouch (restrictive) with Roux-en-Y limb to pouch (malabsorptive) with dumping syndrome physiology
• most effective, higher complication rates
• restrictive
  • laparoscopic adjustable gastric banding
    • silicone band around fundus creates pouch, adjustable through port under skin
  • laparoscopic vertical banded gastroplasty
    • vertical stapled small gastric pouch with placement of silastic ring band
• malabsorptive
  • biliopancreatic diversion with duodenal switch
  • gastrectomy, enterointerostomy, duodenal division closure and duodenoenterostomy

Complications
• perioperative mortality ~1% (anastomotic leak with peritoneal signs, PE)
• obstruction at enterointerostomy (see Complications of Gastric Surgery)
• staple line dehiscence
• dumping syndrome
• cholelithiasis due to rapid weight loss (20-30%)
• band abscess (if long-term)

Complications of Gastric Surgery
• most resolve within 1 yr

Alkaline Reflux Gastritis (see Figure 10A)
• duodenal contents (bilious) reflux into stomach causing gastritis ± esophagitis
• treatment
  • medical: H2-blocker, metoclopramide, cholestyramine (bile acid sequestrant)
  • surgical: conversion of Billroth I or II to Roux-en-Y

Afferent Loop Syndrome (see Figure 10B)
• accumulation of bile and pancreatic secretions causes intermittent mechanical obstruction and distention of afferent limb
• clinical features
  • early postprandial distention, RUQ pain, nausea, bilious vomiting, anemia
• treatment: surgery (conversion to Roux-en-Y increases afferent loop drainage)

Dumping Syndrome (see Figure 10C)
• early – 15 min post-prandial
  • etiology
    • hyperosmotic chyme released into small bowel (fluid accumulation and jejunal distention)
  • clinical features
    • post-prandial symptoms
    • epigastric fullness or pain, emesis, nausea, diarrhea, palpitations, dizziness, tachycardia, diaphoresis
  • treatment
    • small multiple low carbohydrate, low fat, and high protein meals and avoidance of liquids with meals
    • last resort is interposition of antiperistaltic jejunal loop between stomach and small bowel to delay gastric emptying
  • late – 3 h post-prandial
    • etiology: large glucose load leads to large insulin release and hypoglycemia
    • treatment: small snack 2 h after meals

Blind-Loop Syndrome (see Figure 10D)
• bacterial overgrowth of colonic Gram-negative bacteria in afferent limb
• clinical features
  • anemia/weakness, diarrhea, malnutrition, abdominal pain, and hypocalcemia
• treatment: broad-spectrum antibiotics, surgery (conversion to Billroth I)

Postvagotomy Diarrhea (see Figure 10E)
• up to 25%
• bile salts in colon inhibit water resorption
• treatment: medical (cholestyramine), surgical (reversed interposition jejunal segment)
SMALL INTESTINE

Small Bowel Obstruction

Mechanical Small Bowel Obstruction

Etiology

Table 7. Common Causes of SBO

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intussusception</td>
<td>Crohn’s</td>
<td>Adhesions from previous surgeries (75% SBO)</td>
</tr>
<tr>
<td>Gallstones</td>
<td>Radiation stricture</td>
<td>Incarcerated hernia</td>
</tr>
<tr>
<td>Bezars</td>
<td>Adenocarcinoma</td>
<td>Peritoneal carcinomatosis</td>
</tr>
</tbody>
</table>

Pathophysiology

- obstruction → gas & fluid (swallowed or GI secretions) accumulate proximal to site of obstruction and distal decompression → intestinal activity increases to overcome obstruction → colicky pain and diarrhea (initially)
- bowel wall edema and disruption of normal bowel absorptive function can lead to increased intraluminal fluid and transudative fluid loss into peritoneal cavity, electrolyte disturbances
- increase intramural pressure can lead to impaired microvascular perfusion leading to intestinal ischemia and necrosis (strangulated bowel obstruction)
- three types
  - partial SBO: only a portion of intestine is occluded, allows passage of some gas & fluid, less likely to be strangulated
  - complete SBO: progression of pathophysiologic event is much faster than partial SBO
  - closed-loop obstruction: segment of intestine is obstructed both proximally and distally (e.g. volvulus), leading to rapid rise in intraluminal pressure from gas and fluid that cannot escape and rapid progression to strangulation

Risk Factors

- prior abdominal or pelvic surgery, abdominal wall or groin hernia, history of malignancy, prior radiation

Clinical Features

- 1) distinguish mechanical obstruction from ileus; 2) determine etiology of obstruction; 3) recognize partial from complete SBO; 4) differentiate simple from complicated (e.g. strangulated) obstruction
- symptoms: colicky abdominal pain, nausea/vomiting, obstipation
  - vomiting is more prominent with proximal than distal
  - more feculent vomitus suggest more established obstruction because of bacterial overgrowth
  - continue passage of gas and/or stool 6-12 h after onset of symptoms suggest partial than complete obstruction
- signs: abdominal distention (most prominent if obstruction at distal ileum), hyperactive proceeding to minimal bowel sound
  - strangulated obstruction: abdominal pain disproportionate to physical exam findings suggest intestinal ischemia
  - may have tachycardia, localized abdominal tenderness, fever, marked leukocytosis, lactate acidosis

Investigations

- radiological
  - abdominal x-ray (3 views): triad of dilated small bowel (>3 cm in diameter), air-fluid levels on upright film, paucity of air in colon (high sensitivity, low specificity as ileus and LBO can present similarly)
  - CT: discrete transition zone with proximal bowel dilation, distal bowel decompression, and intraluminal contrast does not pass the transition zone
    - most importantly to r/o ischemic bowel/strangulation: pneumatosis intestinalis (free air in bowel wall) & thickened bowel wall, air in portal vein, free intraperitoneal fluids, differential wall enhancements (poor uptake of IV contrast into the wall of the affected bowel)
  - other
    - less used: upper GI series/small bowel series (if no cause apparent, i.e. no hernias, no previous surgeries)
    - may consider U/S or MRI in pregnant patients

Increased Risk of Perforation with Distention as seen on Abdomen Imaging

- Small bowel ≥3 cm
- Distal colon ≥6 cm
- Proximal colon ≥9 cm
- Cecum ≥12 cm

Patients presenting with a SBO in setting of “virgin” abdomen should have surgery ASAP – EXCEPTION: malignant obstruction from history and imaging

In a non-virgin abdomen – adhesional SBOs resolve spontaneously with NGT decompression 70% of time

Top 3 Causes of SBO (in order)

- ABC
  - Adhesions
  - Bulge (hernias)
  - Cancer (neoplasms)

Causes of SBO

- SHAVING
  - Stricture
  - Hernia
  - Adhesions
  - Volvulus
  - Intussusception
  - Neoplasm
- G
  - Gallstones

MUST DO

- Rule out CRC in constipated patient
- Send for TURP in patient with BPH (treat intra-abdominal HTN)
laboratory
- may be normal early in disease course
- BUN, creatinine, hematocrit to assess degree of dehydration
- fluid, electrolyte abnormalities; metabolic alkalosis due to frequent emesis; amylase elevated
- if strangulation: leukocytosis with left shift, lactic acidosis, elevated LDH (late signs)

Treatment
- IV isotonic fluid resuscitation + urine output monitoring with catheter
- SBO related vomiting and decrease PO intake leads to volume depletion
- NG tube in the stomach for gastric decompression; decrease nausea, distention, and risk of aspiration from vomiting
- partial SBO/Crohn's/Carcinomatosis: conservative management with fluid resuscitation and NG tube decompression
- 48 h of watchful waiting; if no improvement or develops complications, surgery
- SBO with history of abdomen/pelvic surgery: conservative management
- 48 h of watchful waiting; if no improvement or develops complications, surgery
- complete SBO/strangulation: urgent surgery to prevent irreversible ischemia
- early post-operative SBO: if bowel function do not return within 3-5 d after surgery; usually partial, extended conservative therapy (2-3 wk) with bowel rest, fluids, and TPN is appropriate
- surgery if presence of peritonitis or complete SBO demonstrated

Prognosis
- related to etiology; mortality: non-strangulating <1%, strangulating 8% (25% if >36 h), ischemic = up to 50%

Prevention
- open surgery has four fold increase in risk of SBO in 5 yr compared to laparoscopic surgery

Functional Small Bowel Obstruction: Paralytic Ileus

Pathogenesis
- temporary, reversible impairment of intestinal motility; mostly frequently caused by:
  - abdominal operations, infections & inflammation, medications (opiates, anesthetics, psychotropics), and electrolyte abnormalities
  - passing gas is the most useful indicator
- NOT the same as intestinal pseudo-obstruction
- chronic pseudo-obstruction refers to specific disorders that affect the smooth muscle and myenteric plexus, leading to irreversible intestinal dysmotility

Clinical Features
- symptoms and signs of intestinal obstruction without mechanical obstruction
  - bowel sounds are diminished or absent (in contrast to initial hyperactive bowel sounds in SBO)

Investigations
- routine post-operative ileus: expected, no investigation needed
- if ileus persists or occurs without abdominal surgery
  - review patient medications (especially opiates)
  - measure serum electrolyte to monitor for electrolyte abnormalities (including extended lytes like Mg, Ca^{2+}, PO_{4})
  - CT scan to rule out abscess or peritoneal sepsis, or to exclude complete mechanical obstruction

Treatment
- most important: NPO + fluid resuscitation
- NGT decompression, correct causative abnormalities (e.g. sepsis, medications, electrolytes), consider TPN for prolonged ileus
- post-operative: gastric and small bowel motility returns by 24-48 h, colonic motility by 3-5 d
- current interest in novel therapies such as gum chewing and pharmacologic therapy (e.g. alvimopan, an opioid antagonists)
# Intestinal Ischemia

## Etiology
- **Acute**
  - arterio-occlusive mesenteric ischemia (AOMI)
  - thrombotic, embolic, extrinsic compression (e.g., strangulating hernia)
  - non-occlusive mesenteric ischemia (NOMI)
    - mesenteric vasoconstriction secondary to systemic hypoperfusion (preserves supply to vital organs)
    - mesenteric venous thrombosis (MVT)
  - consider hypercoagulable state (i.e., rule out malignancy), DVT (prevents venous outflow)
- **Chronic**: usually due to atherosclerotic disease – look for CVD risk factors
- can lead to occlusion in vessels that supplies the small intestine and the large intestine

## Clinical Features
- **Acute**: severe abdominal pain out of proportion to physical findings, vomiting, bloody diarrhea, bloating, minimal peritoneal signs early in course, hypotension, shock, sepsis
- **Chronic**: postprandial pain (from mesenteric angina), fear of eating, weight loss
- Common sites: SMA supplied territory, “watershed” areas of colon – splenic flexure, left colon, sigmoid colon

## Investigations
- **Laboratory**: leukocytosis (non-specific), lactic acidosis (late finding)
  - amylase, LDH, CK, ALP can be used to observe progress
  - hypercoagulability workup if suspect venous thrombosis
- **AXR**: portal venous gas, intestinal pneumatosis, free air if perforation
- **Contrast CT**: thickened bowel wall, luminal dilatation, SMA or SMV thrombus, mesenteric/portal venous gas, pneumatosis
- **CT angiography** is the gold standard for acute arterial ischemia

## Treatment
- Fluid resuscitation, correct metabolic acidosis, NPO, NGT decompression of stomach, prophylactic broad-spectrum antibiotics, avoid vasoconstrictors and digitalis
- Exploratory laparotomy
- Angiogram, embolectomy/thrombectomy, bypass/graft, mesenteric endarterectomy, anticoagulation therapy, percutaneous transluminal angioplasty ± stent
- Segmental resection of necrotic intestine
  - Assess extent of viability; if extent of bowel viability is uncertain, a second look laparotomy 12-24 h later is mandatory

# Tumours of Small Intestine

## Benign Tumours
- 10x more common than malignant
- Usually asymptomatic until large
- Most common sites: terminal ileum, proximal jejunum
- Polyps
  - Adenomas
  - Hamartomas
  - FAP (see Familial Colon Cancer Syndromes, GS33)
  - Juvenile polyps
- Other: leiomyomas, lipomas, hemangiomas

## Malignant Tumours
- Adenocarcinoma
- Carcinoid
- Lymphoma
- Sarcoma

## Carcinoid Syndrome Symptoms
- Flushing
- Diarrhea
- Right-sided heart failure
Table 8. Malignant Tumours of the Small Intestine

<table>
<thead>
<tr>
<th>Adenocarcinoma</th>
<th>Carcinoid</th>
<th>Lymphoma</th>
<th>Metastatic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Usually 50-70 yr M:F</td>
<td>Increased incidence 50-60 yr</td>
<td>Highest incidence in 70s M:F</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Crohn’s, FAP, history of CRC, HNPCC</td>
<td>Crohn’s, celiac disease, autoimmune disease, immunosuppression, radiation therapy, nodular lymphoid hyperplasia</td>
<td>Melanoma, breast, lung, ovary, colon, cervical cancer</td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Early metastasis to lymph nodes 80% metastatic at time of operation</td>
<td>N/V, anemia, GI bleeding, jaundice, weight loss (less common)</td>
<td>Fatigue, weight loss, fever</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain (common)</td>
<td>Often slow-growing Usually asymptomatic, incidental finding</td>
<td>Malabsorption, abdominal pain, anorexia, vomiting, constipation, mass</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Obstruction, bleeding, crampy abdominal pain, intussusception</td>
<td>Rarely – perforation, obstruction, bleeding, intussusception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Carcinoid syndrome (&lt;10%)</td>
<td>Obstruction and bleeding</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Hot flashes, hypotension, diarrhea, bronchoconstriction, right heart failure</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Requires liver involvement: lesion secretes serotonin, kinins, and vasoactive peptides directly to systemic circulation (normally inactivated by liver)</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td>CT abdomen/pelvis Endoscopy</td>
<td>Most found incidentally at surgery for obstruction or appendectomy</td>
<td>CT abdomen/pelvis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider small bowel enteroclysis to look for primary</td>
<td>CT abdomen/pelvis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Serum chromogranin A as a tumour marker</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Elevated 5-HIAA (breakdown product of serotonin) in urine or increased 5-HT in blood</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Radiolabelled octreotide or MIBG scans to search for metastases and locate tumour</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Surgical resection ± chemotherapy</td>
<td>Surgical resection ± chemotherapy Carcinoid syndrome treated with steroids, histamine, octreotide Metastatic risk 2% if size &lt;1 cm, 90% if &gt;2 cm</td>
<td>Low grade: chemotherapy with cyclophosphamide High grade: surgical resection, radiation Palliative: somatostatin, doxorubicin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Palliation</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>5 yr survival 25% (if node positive)</td>
<td>5 yr survival 70%; 20% with liver metastases</td>
<td>5 yr survival 40%</td>
</tr>
<tr>
<td><strong>Origin/Location</strong></td>
<td>Usually in proximal small bowel, incidence decreases distally</td>
<td>Classified based on embryological origin (foregut, midgut, hindgut) Originate from gut enterochromaffin cell Appendix 46%, distal ileum 28%, rectum 17%</td>
<td>Usually distal ileum Proximal jejunum in patients with celiac disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hematogenous spread from breast, lung, kidney Direct extension from cervix, ovaries, colon</td>
</tr>
</tbody>
</table>

**Short Gut Syndrome**

**Definition**
- <200 cm of small bowel causing insufficient intestinal absorption leading to diarrhea, malnutrition, and dehydration

**Risk Factors**
- acute mesenteric ischemia: resection of large amount of bowel at once
- Crohn’s disease: cumulative resections
- malignancies

**Prognostic Factors**
- residual bowel length, residual colon length (reabsorption of water and electrolytes and some reabsorption of nutrients), condition of the remnant small bowel (healthier bowel facilitate better reabsorption), presence of ileocecal valve (delay transition into colon leading to more reabsorption)
- resection of ileum is less tolerated than resection of jejunum (ileum reabsorbs bile salt and vitamin B₁₂)
Therapy
• medical
  † TPN: replenish lost fluid and electrolytes in diarrhea
  † HT2R antagonist or PPI to prevent gastric acid secretion
  † antimotility agent to prolong transit time in the small intestine
  † consider octreotide to decrease GI secretion & cholestyramine for bile acid absorption
• surgical: non-transplant
  † to slow transit time: small bowel segmental reversal, intestinal valve construction, or electrical pacing of small bowel
  † to increase intestinal length:
    † LILT (longitudinal intestinal lengthening and tailoring) procedure
    † STEP (serial transverse enteroplasty procedure) in dilated small bowel
• surgical: transplant
  † indication: life-threatening complication from intestinal failure or long-term TPN
  † liver failure, thrombosis of major central veins, recurrent catheter-related sepsis, recurrent severe dehydration

Abdominal Hernia

• see Hiatus Hernia, GS12

Definition
• defect in abdominal wall causing abnormal protrusion of intra-abdominal contents

Epidemiology
• M:F = 9:1
• lifetime risk of developing a hernia: males 20-25%, females 2%
• frequency of occurrence: 50% indirect inguinal, 25% direct inguinal, 8-10% incisional (ventral), 5% femoral, 3-8% umbilical
• most common surgical disease of males

Risk Factors
• activities which increase intra-abdominal pressure
  † obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, heavy lifting
• congenital abnormality (e.g. patent processus vaginalis, indirect inguinal hernia)
• previous hernia repair, especially if complicated by wound infection
• loss of tissue strength and elasticity (e.g. hiatus hernia, aging, repetitive stress)

Clinical Features
• mass of variable size
• tenderness worse at end of day, relieved with supine position or with reduction
• abdominal fullness, vomiting, constipation
• tenderness worse at end of day, relieved with supine position or with reduction
• mass of variable size
• transmits palpable impulse with coughing or straining

Investigations
• physical examination usually sufficient
• U/S ± CT (CT required for obturator hernias, internal abdominal hernias, and Spigelian and/or femoral hernias in obese patients)

Classification
• complete: hernia sac and contents protrude through defect
• incomplete: partial protrusion through the defect
• internal hernia: sac herniating into or involving intra-abdominal structure
• external hernia: sac protrudes completely through abdominal wall
• strangulated hernia: vascular supply of protruded viscus is compromised (ischemia)
  † requires emergency repair
• incarcerated hernia: irreducible hernia, not necessarily strangulated
• Richter’s hernia: only part of bowel circumference (usually anti-mesenteric border) is incarcerated or strangulated so may not be obstructed
  † a strangulated Richter’s hernia may self-reduce and thus be overlooked, leaving a gangrenous segment at risk of perforation in the absence of obstructive symptoms
• sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)

Indirect Inguinal Hernias: Rule of 5s
5% lifetime incidence in males
5x more common than direct inguinal hernias
5-10x more common in males than females
Generally occur by 5th decade of life

Risk Factors
• obesity, chronic cough, asthma, COPD, pregnancy, constipation, bladder outlet obstruction, ascites, heavy lifting

Clinical Features
• mass of variable size
• tenderness worse at end of day, relieved with supine position or with reduction
• abdominal fullness, vomiting, constipation
• tenderness worse at end of day, relieved with supine position or with reduction
• mass of variable size
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• sliding hernia: part of wall of hernia sac formed by retroperitoneal structure (usually colon)
Anatomical Types
- groin (see Tables 9 and 10)
  - indirect and direct inguinal, femoral (see Figure 14)
  - pantaloon: combined direct and indirect hernias, peritoneum draped over inferior epigastric vessels
- epigastric: defect in linea alba above umbilicus
- incisional: ventral hernia at site of wound closure, may be secondary to wound infection
- other: Littre’s (involving Meckel’s), Amyand’s (containing appendix), lumbar, obturator, peristomal, umbilical, Spigelian (ventral hernia through linea semilunaris)

Complications
- incarceration
- strangulation
  - small, new hernias more likely to strangulate
  - femoral >> indirect inguinal > direct inguinal
- intense pain followed by tenderness
- intestinal obstruction, gangrenous bowel, sepsis
- surgical emergency
- DO NOT attempt to manually reduce hernia if septic or if contents of hernial sac gangrenous
  - will cause closed loop SBO – and EMERGENCY

Treatment
- surgical treatment (herniorrhaphy) is only to prevent strangulation and evisceration, for symptomatic relief, for cosmesis; if asymptomatic can delay surgery
- repair may be done open or laparoscopic and may use mesh for tension-free closure
- most repairs are now done using tension free techniques – a plug in the hernial defect and a patch over it or patch alone
- observation is acceptable for small asymptomatic inguinal hernias

Post-Operative Complications
- recurrence (15–20%)
  - risk factors: recurrent hernia, age >50, smoking, BMI >25, poor pre-operative functional status (ASA ≥ 3 – see Anesthesia and Perioperative Medicine, A4), associated medical conditions: type 2 DM, hyperlipidemia, immunosuppression, any comorbid conditions increasing intra-abdominal pressure
  - less common with mesh/“tension-free” repair
 - scrotal hematoma (3%)
  - painful scrotal swelling from compromised venous return of testes
  - deep bleeding: may enter retroperitoneal space and not be initially apparent
  - difficulty voiding
- nerve entrapment
  - ilioinguinal (causes numbness of inner thigh or lateral scrotum)
  - genital branch of genitofemoral (in spermatic cord)
- stenosis/occlusion of femoral vein
  - acute leg swelling
- ischemic colitis

Groin Hernias

Table 9. Groin Hernias

<table>
<thead>
<tr>
<th></th>
<th>Direct Inguinal</th>
<th>Indirect Inguinal</th>
<th>Femoral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>1% of all men</td>
<td>Most common hernia in men and women</td>
<td>Affects mostly females</td>
</tr>
<tr>
<td>Etiology</td>
<td>Acquired weakness of transversalis fascia</td>
<td>Congenital persistence of processus vaginalis in 20% of adults</td>
<td>Pregnancy – weakness of pelvic floor musculature</td>
</tr>
<tr>
<td></td>
<td>“Wear and tear”</td>
<td>Increased intra-abdominal pressure</td>
<td>Increased intra-abdominal pressure</td>
</tr>
<tr>
<td>Anatomy</td>
<td>Through Hesselbach’s triangle</td>
<td>Medial to inferior epigastric artery</td>
<td>Lateral to inferior epigastric artery</td>
</tr>
<tr>
<td></td>
<td>Usually does not descend into scrotal sac</td>
<td>Often descends into scrotal sac</td>
<td>Often descends into scrotal sac</td>
</tr>
<tr>
<td></td>
<td>(or labia majora)</td>
<td>or labia majora</td>
<td>or labia majora</td>
</tr>
<tr>
<td>Treatment</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
<td>Surgical repair</td>
</tr>
<tr>
<td>Prognosis</td>
<td>3-4% risk of recurrence</td>
<td>&lt;1% risk of recurrence</td>
<td></td>
</tr>
</tbody>
</table>
Table 10. Superficial Inguinal Ring vs. Deep Inguinal Ring*

<table>
<thead>
<tr>
<th>Superficial Inguinal Ring</th>
<th>Deep Inguinal Ring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opening in external abdominal aponeurosis; palpable superior and lateral to pubic tubercle</td>
<td>Opening in transversalis fascia: palpable superior to mid-inguinal ligament</td>
</tr>
<tr>
<td>Medial border: medial crus of external abdominal aponeurosis</td>
<td>Medial border: inferior epigastric vessels</td>
</tr>
<tr>
<td>Lateral border: lateral crus of external oblique aponeurosis</td>
<td>Superior-lateral border: internal oblique and transversus abdominis muscles</td>
</tr>
<tr>
<td>Roof: intercrural fibres</td>
<td>Inferior border: inguinal ligament</td>
</tr>
</tbody>
</table>

*see Basic Anatomy Review, Figure 2, GS2

Appendix

Appendicitis

Epidemiology
- 6% of population, M>F
- 80% between 5-35 yr of age

Pathogenesis
- luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess (walled off by omentum) or peritonitis
- etiology
  - children or young adult: hyperplasia of lymphoid follicles, initiated by infection
  - adult: fibrosis/stricture, fecolith, obstructing neoplasm
  - other causes: parasites, foreign body

Clinical Features
- most reliable feature is progression of signs and symptoms
- low grade fever (38°C), rises if perforation
- abdominal pain then anorexia, N/V
- classic pattern: pain initially periumbilical; constant, dull, poorly localized, then well localized pain over McBurney's point
  - due to progression of disease from visceral irritation (causing referred pain from structures of the embryonic midgut, including the appendix) to irritation of parietal structures
  - McBurney's sign
  - signs
    - inferior appendix: McBurney's sign (see sidebar), Rovsing's sign (palpation pressure to left abdomen causes McBurney's point tenderness). McBurney's sign is present whenever the opening of the appendix at the cecum is directly under McBurney's point; therefore McBurney's sign is present even when the appendix is in different locations
    - retrocecal appendix: psoas sign (pain on flexion of hip against resistance or passive hyperextension of hip)
    - pelvic appendix: obturator sign (flexion then external or internal rotation about right hip causes pain)
- complications
  - perforation (especially if >24 h duration)
  - abscess, phlegmon

Investigations
- laboratory
  - mild leukocytosis with left shift (may have normal WBC counts)
  - higher leukocyte count with perforation
  - β-hCG to rule out ectopic pregnancy
  - urinalysis
- imaging
  - of psoas shadow, RLQ ileus
  - U/S: may visualize appendix, but also helps rule out gynecological causes – overall accuracy 90-94%, can rule in but CANNOT rule out appendicitis (if >6 mm, SENS/SPEC/PPV/PPV 98%)
  - upright CXR, AXR: usually nonspecific – free air if perforated (rarely), calcified fecolith, loss of psoas shadow, RLQ ileus
  - CT scan: thick wall, appendicolith, inflammatory changes – overall accuracy 94-100%, optimal investigation

Watchful Waiting vs. Repair of Inguinal Hernia in Minimally Symptomatic Men: A Randomized Clinical Trial

Outcomes of Laparoscopic vs. Open Repair of Primary Ventral Hernias

McBurney’s Sign
Tenderness 1/3 the distance from the ASIS to the umbilicus on the right side
Inflammatory Bowel Disease

Principles of Surgical Management
- can alleviate symptoms, address complications, improve quality of life
- conserve bowel: resect as little as possible to avoid short gut syndrome
- perioperative management
  - optimize medical status: may require TPN (especially if >7 d NPO) and bowel rest
  - hold immunosuppressive therapy pre-operative, provide pre-operative stress dose of corticosteroid if patient had recent steroid therapy, taper steroids post-operative
  - DVT prophylaxis: heparin (IBD patients at increased risk of thromboembolic events)

Crohn’s Disease

Treatment
- surgery is NOT curative, but over lifetime ~70% of Crohn’s patients will have surgery
- indications for surgical management
  - failure of medical management
  - SBO (due to stricture/inflammation): indication in 50% of surgical cases
  - abscess, fistula (enterocolic, vesicular, vaginal, cutaneous abscess), quality of life, perforation, hemorrhage, chronic disability, failure to thrive (children), perianal disease
- surgical procedures
  - resection and anastomosis/stoma if active or subacute inflammation, perforation, fistula
  - resection margin only has to be free of gross disease (microscopic disease irrelevant to prognosis)
  - stricturoplasty – widens lumen in chronically scarred bowel: relieves obstruction without resecting bowel (contraindicated in acute inflammation)

Complications of Treatment
- short gut syndrome (diarrhea, steatorrhea, malnutrition)
- fistulas
- gallstones (if terminal ileum resected, decreased bile salt resorption → increased cholesterol precipitation)
- kidney stones (loss of calcium in diarrhea → increased oxalate absorption and hyperoxaluria → stones)

Prognosis
- recurrence rate at 10 yr: ileocolic (25-50%), small bowel (50%), colonic (40-50%)
- re-operation at 5 yr: primary resection (20%), bypass (50%), stricturoplasty (10% at 1 yr)
- 80-85% of patients who need surgery lead normal lives
- mortality: 15% at 30 yr
Ulcerative Colitis

• see Gastroenterology, G22

Treatment

• indications for surgical management
  ▪ failure of medical management (including inability to taper steroids)
  ▪ complications: hemorrhage, obstruction, perforation, toxic megacolon (emergency), failure to thrive (children)
  ▪ reduce cancer risk (1-2% risk per yr after 10 yr of disease)
• surgical procedures
  ▪ proctocolectomy and ileal pouch-anal anastomosis (IPAA) ± rectal mucosectomy (operation of choice)
  ▪ proctocolectomy with permanent end ileostomy (if not a candidate for ileoanal procedures)
  ▪ colectomy and IPAA ± rectal mucosectomy
  ▪ in emergency: total colectomy and ileostomy with Hartmann closure of the rectum, rectal preservation

Complications of Treatment

• early: bowel obstruction, transient urinary dysfunction, dehydration (high stoma output), anastomatic leak
• late: stricture, anal fistula/abscess, pouchitis, poor anorectal function, reduced fertility

Prognosis

• mortality: 5% over 10 yr
• total proctocolectomy will completely eliminate risk of cancer
• perforation of the colon is the leading cause of death from ulcerative colitis

LARGE INTESTINE

Large Bowel Obstruction

Mechanical Large Bowel Obstruction

Etiology

Table 11. Common Causes of LBO

<table>
<thead>
<tr>
<th>Intraluminal</th>
<th>Intramural</th>
<th>Extramural</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Adenocarcinoma</td>
<td>Volvulus</td>
</tr>
<tr>
<td>Foreign bodies</td>
<td>Diverticulitis</td>
<td>Adhesions</td>
</tr>
<tr>
<td>IBD stricture</td>
<td>Radiation stricture</td>
<td>Hemias (sigmoid colon in a large groin hemia)</td>
</tr>
</tbody>
</table>

Clinical Features (unique to LBO)

• open loop (10-20%)
  ▪ incompetent ileocecal valve allows relief of colonic pressure as contents reflux into ileum, therefore clinical presentation similar to SBO
• closed loop (80-90%) (dangerous)
  ▪ competent ileocecal valve, resulting in proximal and distal occlusions
  ▪ massive colonic distention → increased pressure in cecum → bowel wall ischemia → necrosis → perforation

Treatment

• surgical correction of obstruction (usually requires resection + temporary diverting colostomy)
• volvulus requires sigmoidoscopic or endoscopic decompression followed by operative reduction if unsuccessful
  ▪ if successful, consider sigmoid resection on same admission
• cecal volvulus can be a true volvulus or a cecal ‘basculé’ (cecum folds anteriorly to the ascending colon producing a flap valve occlusion to cecal emptying) – both need surgical treatment

Prognosis

• overall mortality: 10%
• cecal perforation + feculent peritonitis: 20% mortality
Table 12. Bowel Obstruction vs. Paralytic Ileus

<table>
<thead>
<tr>
<th></th>
<th>SBO</th>
<th>LBO</th>
<th>Paralytic Ileus</th>
</tr>
</thead>
<tbody>
<tr>
<td>N/V</td>
<td>Early, may be bilious</td>
<td>Late, may be feculent</td>
<td>Present</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>Colicky</td>
<td>Colicky</td>
<td>Minimal or absent</td>
</tr>
<tr>
<td>Abdominal Distention</td>
<td>+ (prox SBO), ++ (distal SBO)</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Bowel Sounds</td>
<td>Normal, increased</td>
<td>Absent if secondary ileus (delayed presentation)</td>
<td>Decreased, absent</td>
</tr>
<tr>
<td>AXR Findings</td>
<td>Air-fluid levels</td>
<td>“Ladder” pattern (plicae circularis)</td>
<td>Air throughout small bowel and colon</td>
</tr>
<tr>
<td></td>
<td>Proximal distention (&gt;3 cm)</td>
<td>No colonic gas</td>
<td>“Picture frame” appearance</td>
</tr>
<tr>
<td></td>
<td>+ no colonic gas</td>
<td></td>
<td>Proximal distention + distal decompression</td>
</tr>
</tbody>
</table>

Functional LBO: Colonic Pseudo-obstruction (Ogilvie’s Syndrome)

Definition
- acute pseudo-obstruction
- distention of colon without mechanical obstruction in distal colon
- arises in bedridden patients with serious extra-intestinal illness or trauma
- exact mechanism unknown, likely autonomic motor dysregulation → possibly sympathetic deprivation to colon, unopposed parasympathetic tone, and interruption of sacral parasympathetic tone to distal bowel
- first presents with abdominal distention (>90%) ± tenderness
- later symptoms mimic true obstruction

Associations
- most common: trauma, infection, cardiac (MI, CHF)
- disability (long-term debilitation, chronic disease, bed-bound nursing home patients, paraplegia), drugs (narcotic use, laxative abuse, polypharmacy), other (recent orthopedic or neurosurgery, post-partum, electrolyte abnormalities including hypokalemia, retroperitoneal hematoma, diffuse carcinomatosis)

Clinical Features
- Most prominent is abdominal distention (acute or gradual over 3-7 days)
- Abdominal pain, nausea and vomiting, constipation/diarrhea
- Watch out for fever, leukocytosis, and presence of peritoneal signs

Investigations
- AXR: cecal dilatation – if diameter ≥12 cm, increased risk of perforation

Treatment
- treat underlying cause
- NPO, NGT
- decompression: rectal tube, colonoscopy, neostigmine (cholinergic drug), surgical decompression (ostomy/resection) uncommon
- surgery (extremely rare): if perforation, ischemia, or failure of conservative management

Prognosis
- most resolve with conservative management

Diverticular Disease

Definitions
- diverticulum: abnormal sac-like protrusion from the wall of a hollow organ
- diverticulosis: presence of multiple diverticula
- diverticulitis: inflammation of diverticula
- true (congenital) diverticuli: contain all layers of colonic wall, often right-sided
- false (acquired) diverticuli: contain mucosa and submucosa, often left-sided
# Diverticulosis

**Epidemiology**
- 5-50% of Western population, lower incidence in non-Western countries, M=F
- prevalence is age dependent: <5% by age 40, 30% by age 60, 65% by age 85
- 95% involve sigmoid colon (site of highest pressure)

**Pathogenesis**
- risk factors
  - lifestyle: low-fibre diet (predispose to motility abnormalities and higher intraluminal pressure), inactivity, obesity
  - muscle wall weakness from aging and illness (e.g. Ehler-Danlos, Marfan's)
- high intraluminal pressures cause outpouching to occur at point of greatest weakness, most commonly where vasa recta penetrate the circular muscle layer, therefore increased risk of hemorrhage

**Clinical Features**
- uncomplicated diverticulosis: asymptomatic (70-80%)
- episodic abdominal pain (often LLQ), bloating, flatulence, constipation, diarrhea
- absence of fever/leukocytosis
- no physical exam findings or poorly localized LLQ tenderness
- complications
  - diverticulitis (15-25%): 25% of which are complicated (i.e. abscess, obstruction, perforation, fistula)
  - bleeding (5-15%): PAINLESS rectal bleeding, 30-50% of massive LGIB
  - diverticular colitis (rare): diarrhea, hematochezia, tenesmus, abdominal pain

**Treatment**
- uncomplicated diverticulosis: high fibre, education
- diverticular bleed
  - initially workup and treat as any LGIB
  - if hemorrhage does not stop, resect involved region

---

# Diverticulitis

**Epidemiology**
- 95% left-sided in patients of Western countries, 75% right-sided in Asian populations

**Pathogenesis**
- erosion of the wall by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro or macroscopic perforation
- usually mild inflammation with perforation walled off by pericolic fat and mesentery; abscess, fistula, or obstruction can ensue
- poor containment results in free perforation and peritonitis

**Clinical Features**
- depend on severity of inflammation and whether or not complications are present; hence ranges from asymptomatic to generalized peritonitis
- LLQ pain/tenderness (2/3 of patients) often for several days before admission
- constipation, diarrhea, N/V, urinary symptoms (with adjacent inflammation)
• complications (25% of cases)
  ▪ abscess: palpable tender abdominal mass
  ▪ fistula: colovesical (most common), colorectal, colovaginal, colocutaneous
  ▪ colonic obstruction: due to scarring from repeated inflammation
  ▪ perforation: generalized peritonitis (feculent vs. purulent)
    ▪ recurrent attacks rarely lead to peritonitis
• low-grade fever, mild leukocytosis common, occult or gross blood in stool rarely coexist with acute diverticulitis

Investigations
• AXR, upright CXR
  ▪ localized diverticulitis (ileus, thickened wall, SBO, partial colonic obstruction)
  ▪ free air may be seen in 30% with perforation and generalized peritonitis
• CT scan (test of choice): very useful for assessment of severity and prognosis; usually done with rectal contrast
  ▪ 97% sensitive, 99% specific
  ▪ increased soft tissue density within pericolic fat secondary to inflammation, diverticula
    secondary to inflammation, bowel wall thickening, soft tissue mass (pericolic fluid, abscesses), fistula
  ▪ 10% of diverticulitis cannot be distinguished from carcinoma
• elective evaluations: establish extent of disease and rule out other diagnoses (polyps, malignancy) after resolution of acute episode
  ▪ colonoscopy or barium enema and flexible sigmoidoscopy

Treatment
• uncomplicated: conservative management
• outpatient: clear fluids only until improvement and antibiotics (e.g. ciprofloxacin and metronidazole) 7-10 d to cover gram negative rods and anaerobes (e.g. B. fragilis)
• hospitalize: if severe presentation, inability to tolerate oral intake, significant comorbidities, fail to improve outpatient management
• treat with NPO, IVF, IV antibiotics (e.g. IV ceftriaxone + metronidazole, ampicillin, gentamicin)
• indications for surgery
  ▪ unstable patient with peritonitis
  ▪ Hinchey stage 3-4
  ▪ after 1 attack if immunosuppressed
  ▪ consider after >4 episodes, recent trend is toward conservative management of recurrent mild/moderate attacks
  ▪ complications: generalized peritonitis, free air, abscess, fistula, obstruction, hemorrhage, inability to rule out colon cancer on endoscopy, or failure of medical management
• surgical procedures
  ▪ for emergency or complex cases: Hartmann procedure
    ▪ traditionally, Hartmann procedure was done, with colon resection + colostomy and rectal stump → colostomy reversal in 3-6 mo
    ▪ emerging evidence suggests that for Hinchey stage III acute complicated diverticulitis, laparoscopic peritoneal lavage with drain placement near the affected colon, in addition to IV antibiotics (NO resections), offers lower mortality and morbidity compare to Hartmann procedure. This procedure is gradually becoming standard practice
  ▪ elective cases or minimal contamination of the abdominal cavity: consider colon resection + primary anastomosis

Prognosis
• mortality rates: 6% for purulent peritonitis, 35% for fecal peritonitis
• recurrence rates: 13-30% after first attack, 30-50% after second attack

Table 13. Hinchey Staging and Treatment for Diverticulitis

<table>
<thead>
<tr>
<th>Hinchey Stage</th>
<th>Description</th>
<th>Acute Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Phlegmon/small pericolic abscess</td>
<td>Medical</td>
</tr>
<tr>
<td>2</td>
<td>Large abscess/fistula</td>
<td>Abscess drainage, resection ± primary anastomosis</td>
</tr>
<tr>
<td>3</td>
<td>Feculent peritonitis (ruptured abscess)</td>
<td>Hartmann procedure</td>
</tr>
<tr>
<td>4</td>
<td>Purulent peritonitis</td>
<td>Hartmann procedure</td>
</tr>
</tbody>
</table>
Colorectal Neoplasms

Colorectal Polyps

Definition
- polyp: protuberance into the lumen of normally flat colonic mucosa
- sessile (flat) or pedunculated (on a stalk)

Epidemiology
- 30% of the population have polyps by age 50, 40% by age 60, 50% by age 70

Clinical Features
- 50% in the rectosigmoid region, 50% are multiple
- usually asymptomatic, do not typically bleed, tenesmus, intestinal obstruction, mucus
- usually detected during routine endoscopy or Familial/High risk screening

Pathology
- non-neoplastic
  - hyperplastic: most common non-neoplastic polyp
  - mucosal polyps: small <5 mm, no clinical significance
  - inflammatory pseudopolyps: associated with IBD, no malignant potential
  - submucosal polyps: lymphoid aggregates, lipomas, leiomyomas, carcinoids
- neoplastic
  - lipomas, leiomyomas, carcinoids
  - hamartomas: juvenile polyps (large bowel), Peutz-Jegher syndrome (small bowel)
  - malignant risk due to associated adenomas (large bowel)
  - low malignant potential → most spontaneously regress or autoamputate
  - adenomas: premalignant, considered carcinoma in situ IF high grade dysplasia
  - some may contain invasive carcinoma (“malignant polyp” – 3-9%): invasion into submucosa
    - malignant potential: villous > tubulovillous > tubular

Table 14. Characteristics of Tubular vs. Villous Polyps

<table>
<thead>
<tr>
<th></th>
<th>Tubular</th>
<th>Villous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>Common (60-80%)</td>
<td>Less common (10%)</td>
</tr>
<tr>
<td>Size</td>
<td>Small (&lt;2 cm)</td>
<td>Large (usually &gt;2 cm)</td>
</tr>
<tr>
<td>Attachment</td>
<td>Pedunculated</td>
<td>Sessile</td>
</tr>
<tr>
<td>Malignant Potential</td>
<td>Lower</td>
<td>Higher</td>
</tr>
<tr>
<td>Distribution</td>
<td>Even</td>
<td>Left-sided predominance</td>
</tr>
</tbody>
</table>

Investigations
- colonoscopy is the gold standard for diagnosis and treatment of colonic polyps
- CT colonography: increasing in availability; patients still require bowel prep and will require colonoscopy if polyps are identified
- other: flexible sigmoidoscopy if polyps are detected, proceed to colonoscopy for examination of entire bowel and biopsy

Treatment
- indications: symptoms, malignancy or risk of malignancy (i.e. adenomatous polyps)
- endoscopic removal of entire growth
- indications for segmental resection for malignant polyps: 1) lymphovascular invasion; 2) tumour budding; 3) positive resection margin; 4) poorly differentiated cells; 5) evidence of regional or distant metastases on staging. Most of these cases are usually discussed at multidisciplinary tumour boards
- follow-up endoscopy 1 yr later, then every 3-5 yr

Familial Colon Cancer Syndromes

FAMILIAL ADENOMATOUS POLYPOSIS

Pathogenesis
- autosomal dominant inheritance, mutation in adenomatous polyposis coli (APC) gene on chromosome 5q21

Clinical Features
- hundreds to thousands of colorectal adenomas usually by age 20 (by 40s in attenuated FAP)
extracolonic manifestations
- carcinoma of small bowel (i.e. polyps in colon), bile duct, pancreas, stomach, thyroid, adrenal, small bowel
- congenital hypertrophy of retinal pigment epithelium presents early in life in 2/3 of patients; 97% sensitivity
- virtually 100% lifetime risk of colon cancer (because of number of polyps)
- variants
  - Gardner’s syndrome: FAP + extra-intestinal lesions (sebaceous cysts, osteomas, desmoid tumours)
  - Turcot syndrome: FAP + CNS tumours (childhood cerebellar medulloblastoma)

Investigations
- genetic testing (80-95% sensitive, 99-100% specific)
- if no polyposis found: annual flexible sigmoidoscopy from puberty to age 50, then routine screening
- if polyposis or APC gene mutation found: annual colonoscopy and consider surgery (see Figure 16); consider upper endoscopy to evaluate for periampullary tumours

Treatment
- surgery indicated by age 17-20
- total proctocolectomy with ileostomy or total colectomy with ileorectal anastomosis
- doxorubicin-based chemotherapy
- NSAIDs for intra-abdominal desmoids

HEREDITARY NON-POLYPOSIS COLORECTAL CANCER – LYNCH SYNDROME

Pathogenesis
- autosomal dominant inheritance, mutation in a DNA mismatch repair gene (MSH2, MSH6, MLH1) resulting in microsatellite genomic instability and subsequent mutations
- microsatellite instability account for approximately 15% of all colorectal cancers

Clinical Features
- early age of onset, right > left colon, synchronous and metachronous lesions
- mean age of cancer presentation is 44 yr, lifetime risk 70-80% (M>F)
  - HNPCC I: hereditary site-specific colon cancer
  - HNPCC II: cancer family syndrome – high rates of extracolonic tumours (endometrial, ovarian, hepatobiliary, small bowel)

Diagnosis
- Amsterdam Criteria
  - 3 or more relatives with verified Lynch syndrome associated cancers, and 1 must be 1st degree relative of the other 2
  - 2 or more generations involved
  - 1 case must be diagnosed before 50 yr old
  - FAP is excluded
- genetic testing (80% sensitive) – colonoscopy mandatory even if negative
  - refer for genetic screening individuals who fulfill EITHER the Amsterdam Criteria (as above) OR the revised Bethesda Criteria (see sidebar)
- colonoscopy (starting age 20) annually
- surveillance for extracolonic lesions

Treatment
- total colectomy and ileorectal anastomosis with annual proctoscopy

Colorectal Carcinoma

Epidemiology
- 4th most common cancer (after lung, prostate, and breast), 2nd most common cause of cancer death

Risk Factors
- most patients have no specific risk factors
- age >50 (dominant risk factor in sporadic cases), mean age is 70
- genetic: FAP, HNPCC, family history of CRC
- colonic conditions
  - adenomatous polyps (especially if >1 cm, villous, multiple)
  - IBD (especially UC: risk is 1-2%/yr if UC >10 yr)
  - previous colorectal cancer (also gonadal or breast)
• diet (increased fat, red meat, decreased fibre) and smoking
• DM and acromegaly (insulin and IGF-1 are growth factors for colonic mucosal cells)

Pathogenesis
• adenoma–carcinoma sequence; rarely arise de novo

Clinical Features
• often asymptomatic
• hematochezia/melena, abdominal pain, change in bowel habits
• others: weakness, anemia, weight loss, palpable mass, obstruction
• 20% patients have distant metastatic disease at time of presentation
• spread
  ▪ direct extension, lymphatic, hematogenous (liver most common, lung, bone, brain; tumour of distal rectum → IVC → lungs)
  ▪ peritoneal seeding: ovary, Blumer’s shelf (pelvic cul-de-sac)

Table 15. Clinical Presentation of CRC

<table>
<thead>
<tr>
<th>Right Colon</th>
<th>Left Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>25%</td>
<td>35%</td>
</tr>
<tr>
<td>Pathology</td>
<td>Exophytic lesions with occult bleeding</td>
<td>Annular, invasive lesions</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Weight loss, weakness, rarely obstruction</td>
<td>Constipation ± overflow (alternating bowel patterns), abdominal pain, decreased stool caliber, rectal bleeding</td>
</tr>
<tr>
<td>Signs</td>
<td>Fe-deficiency anemia, RLQ mass (10%)</td>
<td>BRBPR, LBO</td>
</tr>
</tbody>
</table>

Investigations
• colonoscopy (best), look for synchronous lesions (3-5% of patients); alternative: air contrast barium enema (‘apple core’ lesion) + sigmoidoscopy
• if a patient is FOBT +ve, or has microcytic anemia or has a change in bowel habits, do colonoscopy
• laboratory: CBC, urinalysis, liver enzymes, liver function tests, carcinoembryonic antigen (CEA) (pre-operative for baseline, >5 ng/mL have worse prognosis)
• staging (see Table 16 and sidebar GS35): CT chest/abdomen/pelvis; bone scan, CT head only if lesions suspected
• rectal cancer: pelvic MRI or endorectal U/S to determine T and N stage

Table 16. TNM Classification System for Staging of Colorectal Carcinoma (AJCC/IUCC 2010)

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Tis Carcinoma in situ</td>
<td>N1</td>
<td>M1</td>
</tr>
<tr>
<td>T1 Invasion into submucosa</td>
<td>N2</td>
<td>M1</td>
</tr>
<tr>
<td>T2 Invasion into muscularis propria</td>
<td>N3</td>
<td>M1</td>
</tr>
<tr>
<td>T3 Invasion through muscularis propria and into serosa</td>
<td>N4</td>
<td>M1</td>
</tr>
<tr>
<td>T4 Invasion into adjacent structures or organs</td>
<td>N5</td>
<td>M1</td>
</tr>
</tbody>
</table>

Treatment
• colon cancer
  ▪ wide surgical resection of lesion and regional lymphatic drainage; usually colectomy with primary anastomosis
  ▪ curative: wide resection of lesion (5 cm margins) with nodes and mesentery
  ▪ palliative: if distant spread, local control for hemorrhage or obstruction
  ▪ care is taken to not spread tumour by unnecessary palpation
  ▪ cancer-bearing portion of colon is removed according to vascular distribution of segment
  ▪ adjuvant chemotherapy (5-FU or oral capcitabine with oxaliplatin) for stage III and is considered in select stage II patients

• rectal cancer
  ▪ choice of operation depends on individual case; types of operations
  ▪ low anterior resection of rectum (LAR): curative procedure of choice if adequate distal margins; uses technique of total mesorectal excision
  ▪ abdominoperineal resection of rectum (APR): if adequate distal margins cannot be obtained; involves the removal of distal sigmoid colon, rectum, and anus – permanent end colostomy required
  ▪ local excision: for select T1 lesions only
  ▪ palliative procedures involve proximal diversion with an ostomy for obstruction and radiation for bleeding or pain
  ▪ adjuvant therapy
    ▪ combined neoadjuvant chemoradiation therapy followed by post-operative adjuvant chemotherapy for stages II and III

Figure 18. APR vs. LAR

APR removes distal sigmoid colon, rectum, and anus; permanent end colostomy required
LAR removes distal sigmoid and rectum with anastomosis of distal colon to anus
Follow-Up
• currently there are no data suggesting optimal follow-up
• combination of periodic CT chest/abdomen/pelvis, CEA, and colonoscopy is recommended
• CEA to monitor for initial response to treatment, and to assess for recurrence q3mo (not a screening test)
• intensive follow-up improves overall survival in low-risk patients

Other Conditions of the Large Intestine

Angiodysplasia
Definition
• vascular anomaly: focal submucosal venous dilatation and tortuosity

Clinical Features
• most frequently in right colon of patients >60 yr old
• bleeding typically intermittent, rarely massive, not usually hypotensive (melena, anemia, guaiac positive stools)

Investigations
• colonoscopy: cherry red spots, branching pattern from central vessel
• angiography: early-filling vein, vascular tuft, delayed emptying vein; rarely active bleeding
• RBC technetium-99 scan
• barium enema is contraindicated (obscures other x-rays, i.e. angiogram)

Treatment
• none if asymptomatic
• cautery, right hemicolectomy, embolization, vasopressin infusion, sclerotherapy, band ligation, laser, octreotide, and rarely segmental resection if other treatments fail

Volvulus
Definition
• rotation of segment of bowel about its mesenteric axis
• sigmoid (65%), cecum (30%), transverse colon (3%), splenic flexure (2%)
• 5-10% of large bowel obstruction; 25% of intestinal obstruction during pregnancy

Risk Factors
• age (50% of patients >70 yr: stretching/elongation of bowel with age is a predisposing factor)
• high fibre diet (can cause elongated/redundant colon), chronic constipation, laxative abuse, pregnancy, bedridden, institutionalization (less frequent evacuation of bowels)
• congenital hypermobile cecum

Clinical Features
• symptoms due to bowel obstruction (see Large Bowel Obstruction, GS30) or intestinal ischemia (see Intestinal Ischemia, GS24)
• colicky abdominal pain, persistence of pain between spasms, abdominal distention, vomiting

Investigations
• AXR (classic findings): “omega”, “bent inner-tube”, “coffee-bean” signs
• barium/Gastrografin* enema: “ace of spades” (or “bird’s beak”) appearance due to funnel-like luminal tapering of lower segment towards volvulus
• sigmoidoscopy or colonoscopy as appropriate
• CT

Treatment
• initial supportive management (same as initial management for bowel obstruction (see Large Bowel Obstruction, GS30)
• cecum
  • nonsurgical
  • may attempt colonoscopic detorsion and decompression
  • surgical
  • right colectomy + ileotransverse colonic anastomosis

5-yr Survival Rates for CRC
<table>
<thead>
<tr>
<th>Stage</th>
<th>Colon</th>
<th>Rectum</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>74%</td>
<td>74%</td>
</tr>
<tr>
<td>IIA</td>
<td>67%</td>
<td>64%</td>
</tr>
<tr>
<td>IIB</td>
<td>59%</td>
<td>52%</td>
</tr>
<tr>
<td>IIC</td>
<td>37%</td>
<td>32%</td>
</tr>
<tr>
<td>IIIA</td>
<td>73%</td>
<td>74%</td>
</tr>
<tr>
<td>IIIB</td>
<td>46%</td>
<td>45%</td>
</tr>
<tr>
<td>IIIC</td>
<td>28%</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>
• sigmoid
  • nonsurgical
    • decompression by flexible sigmoidoscopy and insertion of rectal tube past obstruction
    • subsequent elective surgery recommended (50-70% recurrence)
  • surgical: Hartmann procedure (if urgent)
    • indications: strangulation, perforation, or unsuccessful endoscopic decompression

## Toxic Megacolon

### Pathogenesis
- extension of inflammation into smooth muscle layer causing paralysis
- damage to myenteric plexus and electrolyte abnormalities are not consistently found

### Etiology
- inflammatory bowel disease (ulcerative colitis > Crohn's disease)
- infectious colitis: bacterial (C. difficile, Salmonella, Shigella, Campylobacter), viral (cytomegalovirus), parasitic (E. histolytica)

### Clinical Features
- infectious colitis usually present for >1 wk before colonic dilatation
- diarrhea ± blood (but improvement of diarrhea may portend onset of megacolon)
- abdominal distention, tenderness, ± local/general peritoneal signs (suggest perforation)
- triggers: hypokalemia, constipating agents (opioids, antidepressants, loperamide, anticholinergics), barium enema, colonoscopy

### Diagnostic Criteria
- must have both colitis and systemic manifestations for diagnosis
- radiologic evidence of dilated colon
- three of: fever, HR >120, WBC >10.5, anemia
- one of: fluid and electrolyte disturbances, hypotension, altered LOC

### Investigations
- CBC (leukocytosis with left shift, anemia from bloody diarrhea), electrolytes, elevated CRP, ESR
- metabolic alkalosis (volume contraction and hypokalemia) and hypoalbuminemia are late findings
- AXR: dilated colon >6 cm (right > transverse > left), loss of haustra
- CT: useful to assess underlying disease

### Treatment
- NPO, NGT, stop constipating agents, correct fluid and electrolyte abnormalities, transfusion
- serial AXRs
- broad-spectrum antibiotics (reduce sepsis, anticipate perforation)
- aggressive treatment of underlying disease (e.g. steroids in IBD, metronidazole for C. difficile)
- indications for surgery (50% improve on medical management)
  • worsening or persisting toxicity or dilation after 48-72 h
  • severe hemorrhage, perforation
  • high lactate and WBC especially for C. difficile
- procedure: subtotal colectomy + end ileostomy (may be temporary, with second operation for re-anastomosis later)

### Prognosis
- average 25-30% mortality

## Fistula

### Definition
- abnormal communication between two epithelialized surfaces (e.g. enterocutaneous, colovesical, aortoenteric, entero-enteric)

### Etiology
- foreign object erosion (e.g. gallstone, graft)
- inflammatory states (e.g. infection, IBD [especially Crohn’s], diverticular disease)
- iatrogenic/surgery (e.g. post-operative anastomotic leak, radiation)
- congenital, trauma
- neoplastic

### Investigations
- U/S, CT scan, fistulogram
- measure amount of drainage from fistula

### Why Fistulae Stay Open
- FRIENDO
  - Foreign body
  - Radiation
  - Infection
  - Epithelialization
  - Neoplasm
  - Distal obstruction (most common)
  - Others: increased flow, steroids (may inhibit closure, usually will not maintain fistula)
Treatment
• decrease secretion: octreotide/somatostatin/omeprazole
• surgical intervention: dependent upon etiology (for non-closing fistulas); uncertainty of diagnosis

Stomas
Definition
• an opening of the GI tract onto the surface of the abdomen wall

Ileostomy
• usually positioned in RLQ; ileum is brought through rectus abdominus muscles
• indications: after proctocolectomy for ulcerative colitis, in some cases of Crohn’s disease or familial polyposis
• conventional ileostomy: discharges small quantities of liquid material continuously, appliance (plastic bag attached to a sheet of protective material) required at all times
• continent ileostomy: reservoir is constructed from distal ileum, emptied by inserting catheter into stoma several times a day; rarely used, has mostly been replaced by ileal pouch anal anastomosis

Colostomy
• indications: to decompress an obstructed colon, to protect a distal anastomosis after resection, or to evacuate stool after distal colon or rectum is removed
• colostomies can be done by making an opening in a loop of colon (loop colostomy) or by dividing the colon and bringing out one end (end colostomy)
• most common permanent colostomy is a sigmoid colostomy – expels stool once per day, no appliance required
• chronic paracolostomy hernia is a common complication

Complications (10%)
• obstruction: herniation, stenosis (skin and abdominal wall), adhesive bands, volvulus
• peri-ileostomy abscess and fistula
• skin irritation
• prolapse or retraction
• diarrhea (excessive output)

Hemorrhoids
Etiology
• vascular and connective tissue complexes form a plexus of dilated veins (cushion)
  ▪ internal: superior hemorrhoidal veins, above dentate line, portal circulation
  ▪ external: inferior hemorrhoidal veins, below dentate line, systemic circulation

Risk Factors
• increased intra-abdominal pressure: chronic constipation, pregnancy, obesity, portal HTN, heavy lifting
Clinical Features and Treatment
• internal hemorrhoids
  • engorged vascular cushions usually at 3, 7, 11 o'clock positions (patient in lithotomy position)
  • PAINLESS rectal bleeding, anemia, prolapse, mucus discharge, pruritus, burning pain, rectal fullness
    • 1st degree: bleed but do not prolapse through the anus
      – treatment: high fibre/bulk diet, sitz baths, steroid cream, parnixone (Anusol®), rubber band ligation, sclerotherapy, photocoagulation
    • 2nd degree: bleed, prolapse with straining, spontaneous reduction
      – treatment: rubber band ligation, photocoagulation
    • 3rd degree: bleed, prolapse, requires manual reduction
      – treatment: same as 2nd degree, but may require closed haemorroidectomy
    • 4th degree: bleed, permanently prolapsed, cannot be manually reduced
      – treatment: closed haemorroidectomy

  • external hemorrhoids
    • dilated venules usually mildly symptomatic
    • PAIN after bowel movement, associated with poor hygiene
    • medical treatment: dietary fibre, stool softeners, steroid cream (short course), parnixone (Anusol®), avoid prolonged straining
    • thrombosed hemorrhoids are very painful
    • resolve within 2 wk, may leave excess skin = perianal skin tag
    • treatment: consider surgical decompression within first 48 h of thrombosis, otherwise medical treatment

Table 17. Signs and Symptoms of Internal vs. External Hemorrhoids

<table>
<thead>
<tr>
<th>Internal Hemorrhoids</th>
<th>External Hemorrhoids</th>
</tr>
</thead>
<tbody>
<tr>
<td>Painless BRBPR</td>
<td>Sudden severe perianal pain</td>
</tr>
<tr>
<td>Rectal fullness or discomfort</td>
<td>Perianal mass</td>
</tr>
<tr>
<td>Mucus discharge</td>
<td></td>
</tr>
</tbody>
</table>

Anal Fissures

Definition
• tear of anal canal below dentate line (very sensitive squamous epithelium)
• 90% posterior midline, 10% anterior midline
• if off midline: consider other possible causes such as IBD, STIs, TB, leukemia, or anal carcinoma
• repetitive injury cycle after first tear
  • sphincter spasm occurs preventing edges from healing and leads to further tearing
  • ischemia may ensue and contribute to chronicity

Etiology
• forceful dilation of anal canal: large, hard stools and irritant diarrheal stools
• tightening of anal canal secondary to nervousness/pain leads to further tearing
• others: habitual use of cathartics, childbirth

Clinical Features
• acute fissure
  • very painful bright red bleeding especially after bowel movement, sphincter spasm on limited DRE
  • treatment is conservative: stool softeners, bulking agent, sitz baths (heals 90%)
• chronic fissure (anal ulcer)
  • triad: tissue, sentinel skin tags, hypertrophied papillae
  • treatment
    • stool softeners, bulking agents, sitz baths
    • topical nitroglycerin or nifedipine: increases local blood flow, promoting healing and relieves sphincter spasm
    • lateral internal anal sphincterotomy (most effective): objective is to relieve sphincter spasm  ➔ increases blood flow and promotes healing; but 5% chance of fecal incontinence therefore not commonly done
  • alternative treatment
    • botulinum toxin: inhibits release of acetylcholine (ACh), reducing sphincter spasm

Anorectal Abscess

Definition
• infection in one or more of the anal spaces
• usually bacterial infection of blocked anal gland at the dentate line
  • E. coli, Proteus, Streptococci, Staphylococci, Bacteroides, anaerobes
Figure 22. Different types of perianal abscesses

Clinical Features
- throbbing pain that may worsen with straining and ambulation
- abscess can spread vertically downward (perianal), vertically upward (supralevator), or horizontally (ischiorectal)
- tender perianal/rectal mass on exam

Treatment
- I&D
  - curative in 50% of cases
  - 50% develop anorectal fistulas
- may require antibiotics if diabetic, heart murmur, or cellulitis

Fistula-In-Ano

Definition
- anal fistula from rectum to perianal skin
- an inflammatory tract with internal os at dentate line, external os on skin

Etiology
- see Fistula, GS38
- same perirectal process as an anal abscess, therefore usually associated with an abscess
- other causes: post-operative, trauma, anal fissure, malignancy, radiation proctitis

Clinical Features
- intermittent or constant purulent discharge from perianal opening
- pain
- palpable cord-like tract

Treatment
- identification
  - internal opening
    - Goodsall’s rule
      - fistulas originating anterior to a transverse line through the anus will have a straight course and exit anteriorly, whereas those originating posterior to the transverse line will begin in the midline and have a curved tract
  - fistulous tract
    - probing or fistulography under anesthesia
- surgery
  - fistulotomy: unroof tract from external to internal opening, allow drainage, heals by secondary intention
  - low lying fistula (does not involve external sphincter) → primary fistulotomy
  - high lying fistula (involves external sphincter) → staged fistulotomy with Seton suture placed through tract
    - promotes drainage
    - promotes fibrosis and decreases incidence of incontinence
    - delineates anatomy
    - usually done to spare muscle cutting
Post-Operative
- sitz baths, irrigation, and packing to ensure healing proceeds from inside to outside

Complications
- recurrence
- rarely fecal incontinence

Pilonidal Disease

Definition
- chronic recurring abscess or chronic draining sinus in sacrococcygeal area

Epidemiology
- occurs most frequently in young men age 15-40 yr; rare in >50 yr

Etiology
- obstruction of the hair follicles in this area → formation of cysts, sinuses, or abscesses

Clinical Features
- asymptomatic until acutely infected, then pain/tenderness, purulent discharge, inspissated hair

Treatment
- acute abscess
  - I&D (often performed by primary care doctors)
  - wound packed open
  - 40% develop chronic pilonidal sinuses
- surgery
  - indication: failure of healing after I&D, recurrent disease, complex disease
    - pilonidal cystotomy: excision of sinus tract and cyst; wound closed by secondary intention, primary closure with tissue flap, or marsupialization (cyst edge sewn to surrounding tissue to leave sinus tract open)

Rectal Prolapse

Definition
- protrusion of some or all of rectal mucosa through external anal sphincter

Epidemiology
- extremes of ages: <5 yr old and >5th decade
- 85% women

Etiology
- lengthened attachment of rectum secondary to constant straining
- 2 types
  I. false/partial/mucosal: protrusion of mucosa only, radial furrows at junction with anal skin; most common type of rectal prolapse in childhood
  II. true/complete (most common): full thickness extrusion of rectal wall, concentric folds in:
    - first degree: prolapse includes mucocutaneous junction
    - second degree: without involvement of mucocutaneous junction
    - third degree (internal intussusception): prolapse is internal, concealed, or occult

Risk Factors
- gynecological surgery
- chronic neurologic/psychiatric disorders affecting motility

Clinical Features
- extrusion of mass with increased intra-abdominal pressure
  - straining, coughing, laughing, Valsalva
  - difficulty in bowel regulation
  - tenesmus, constipation, fecal incontinence
  - permanently extruded rectum with excoriation, ulceration, and constant soiling
  - may be associated with urinary incontinence or uterine prolapse

Treatment
- Type I
  - conservative: gentle manual reduction of prolapsed area, especially in children
  - mucosectomy with excision of redundant mucosa, mostly in adults
- Type II
  - conservative: reduce if possible
  - surgery: abdominal, perineal, transsacral approaches
**Anal Neoplasms**

**ANAL CANAL**

* Squamous Cell Carcinoma of Anal Canal (Above Dentate Line)*
  - most common tumour of anal canal (75%)
  - anus prone to human papillomavirus (HPV) infection, therefore at risk for anal squamous intra-epithelial lesions (ASIL)
    - high grade squamous intra-epithelial lesion (HSIL) and low grade squamous intra-epithelial lesion (LSIL) terminology used
  - clinical features: anal bleeding, pain, mass, ulceration, pruritus; 25% asymptomatic
  - treatment: chemotherapy ± radiation ± surgery
  - prognosis: 80% 5-yr survival

*Malignant Melanoma of Anal Canal*
  - 3rd most common site for primary malignant melanoma after skin, eyes
  - aggressive, distant metastases common at time of diagnosis
  - treatment: wide excision or APR ± chemoradiation
  - prognosis: <5% 5 yr survival

**ANAL MARGIN**
  - clinical features and treatment as for skin tumours elsewhere
  - squamous and basal cell carcinoma, Bowen's disease (SCC in situ), and Paget's disease

---

**Liver**

**Liver Cysts**

**Table 18. Characteristics of Liver Cysts**

<table>
<thead>
<tr>
<th>Description</th>
<th>Simple Cysts</th>
<th>Polycystic Liver Disease</th>
<th>Choledochal Cysts</th>
<th>Hydatid (Cystic Echinococcosis)</th>
<th>Cystadenoma (Premalignant)/Cystadenocarcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contain clear fluid that do not communicate with the intrahepatic biliary tree</td>
<td>Several cysts that replace much of the liver</td>
<td>Congenital malformations of pancreaticobiliary tree high risk of malignancy majority present before age 10</td>
<td>Infection with parasite Echinococcus granulosus associated with exposure to dogs, sheep, and cattle in Southern Europe, Middle East, Australasia, South America</td>
<td>Rare cystic tumours that occur in the liver parenchyma or the extrahepatic bile ducts Cystadenocarcinoma is an invasive carcinoma</td>
<td></td>
</tr>
<tr>
<td>Usually asymptomatic may have multiple simple cysts</td>
<td>Progressive 50% associated with polycystic kidney disease</td>
<td>Recurrent abdominal pain Intermittent jaundice RUQ mass Cholangitis Pancreatitis</td>
<td>Asymptomatic mass chronic pain Hepatomegaly</td>
<td>Upper abdominal mass Abdominal pain Anorexia</td>
<td></td>
</tr>
</tbody>
</table>

Figure 26. Anatomy of liver
Liver Abscesses

Etiology
- **types**
  - pyogenic (bacterial): most common etiology; most often polymicrobial – *E. coli*, *Klebsiella*, *Proteus*, *Strep. milleri*
  - parasitic (amoebic): *Entamoeba histolytica*, *Echinococcal cyst*
  - fungal: *Candida*
- sources: direct spread from biliary tract infection, portal spread from GI infection, systemic infection (e.g. endocarditis)

Clinical Features
- fever, malaise, chills, anorexia, weight loss, abdominal pain, nausea
- RUQ tenderness, hepatomegaly, jaundice

Investigations
- leukocytosis, anemia, elevated liver enzymes, hemagglutination titres for *Entamoeba* antibodies
- U/S, CXR (right basilar atelectasis/effusion), CT, cyst aspiration with C&S

Treatment
- treat underlying cause
- generally will treat initially with antibiotics alone, and add surgical or percutaneous drainage and IV antibiotics for larger abscesses (initially ceftriaxone + metronidazole or piperacillin/tazobactam)

Prognosis
- overall mortality 15% – higher rate if delay in diagnosis, multiple abscesses, malnutrition

Neoplasms

BENIGN LIVER NEOPLASMS

Hemangioma (cavernous)
- pathogenesis: most common benign hepatic tumour; results from malformation of angioblastic fetal tissue
- risk factors: F:M = 3:1
• clinical features
  - usually small and asymptomatic
  - consumptive coagulopathy if giant (in children)
• investigations
  - contrast CT (well-demarcated hypodense mass with peripheral enhancement and delayed venous emptying), U/S (homogenous hyperechoic mass), arteriography (rarely used; “cotton wool" appearance), MRI
  - avoid biopsy: may result in hemorrhage
• treatment
  - usually none unless tumour bleeds or is symptomatic, then excision by lobectomy or enucleation

Focal Nodular Hyperplasia
• pathogenesis: unclear, may be regenerative response to hyperperfusion from anomalous arteries at centre of nodule
• risk factors: female, age 20-50
• clinical features: asymptomatic, rarely grows or bleeds, no malignant potential
• investigations: central stellate scar on CT scan; MRI, biopsy may be required
• treatment: may be difficult to distinguish from adenoma/fibrolamellar HCC (malignant potential) → often resected

Adenoma
• definition: benign glandular epithelial tumour
• risk factors: female, age 20-50, estrogen (OCP, pregnancy)
• clinical features: asymptomatic, 25% present with RUQ pain or mass, may present with bleeding
• investigations: CT (well-demarcated masses, often heterogeneous enhancement on arterial phase, isodense on venous phase without washout of contrast), U/S, MRI, biopsy often needed
• treatment
  - stop anabolic steroids or OCP
  - excise, especially if large (>5 cm), due to risk of transformation to hepatocellular carcinoma and spontaneous rupture/hemorrhage

MALIGNANT LIVER NEOPLASMS
Primary
• usually hepatocellular carcinoma (HCC)/hepatoma
• others include angiosarcoma, hepatoblastoma, hemangiendothelioma
• epidemiology: 3rd leading cause of cancer death worldwide, 9th in United States; highest in Africa, China, Taiwan
• risk factors
  - chronic liver inflammation: chronic hepatitis B (inherently oncogenic) and hepatitis C, cirrhosis (especially macronodular), hemochromatosis, α1-antitrypsin deficiency
  - medications: OCPs (3x increased risk), steroids
  - smoking, alcohol, Betel nuts
  - chemical carcinogens ( aflatoxin, microcystin, vinyl chloride – associated with angiosarcoma)
• clinical features
  - RUQ discomfort, right shoulder pain
  - jaundice, weakness, weight loss, ± fever (if central tumour necrosis)
  - hepatomegaly, bruist, hepatic friction rub
  - ascites with blood (sudden intra-abdominal hemorrhage)
  - paraneoplastic syndromes – hypoglycemia, hypercalcemia, erythrocytosis, watery diarrhea
  - metastasis: lung, bone, brain, peritoneal seeding
• investigations
  - elevated ALP, bilirubin, and α-fetoprotein (80% of patients)
  - U/S (poorly-defined margins with internal echos), triphasic CT (enhancement on arterial phase and washout on portal venous phase), MRI
  - liver enzyme and liver function tests: AST, ALT, ALP, bilirubin, albumin, INR
• treatment
  - cirrhosis is a relative contraindication to tumour resection due to decreased hepatic reserve
  - surgical: resection (10% of patients have resectable tumours)
  - liver transplant; may use bridging therapy while awaiting transplant
• absolute contraindications: extrahepatic disease, vascular invasion
• relative contraindications: dependent on liver transplant protocol based on staging criteria followed by transplant centre
• non-surgical: radiofrequency ablation, percutaneous ethanol injection, transcatheter arterial chemoembolization (TACE), chemotherapy (consider sorafenib for HCC; pre-operative chemotherapy for hepatoblastoma is standard of care), radiotherapy
Secondary

- metastases to the liver are the most common malignant tumours found in the liver
- etiology
  - GI (colorectal most common), lung, breast, pancreas, ovary, uterus, kidney, gallbladder, prostate
- treatment
  - hepatic resection for metastatic colorectal liver metastases if control of primary is possible, no extrahepatic or extrapulmonary metastases and if possibility of “curative” resection
  - possible chemotherapy
- prognosis: 30-40% 5 yr survival with a “curative” resection; prognosis same if metastases are multilobar compared with confined to one lobe

Liver Transplantation

<table>
<thead>
<tr>
<th>Parenchymal Disease</th>
<th>Cholestatic Disease</th>
<th>Inborn Errors</th>
<th>Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic hepatitis B or C*</td>
<td>Biliary atresia**</td>
<td>C1q-antitrypsin deficiency</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td>Alcoholic cirrhosis</td>
<td>Primary biliary cirrhosis</td>
<td>Wilson’s disease</td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>Sclerosing cholangitis</td>
<td>Hemochromatosis</td>
<td></td>
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<tr>
<td>Budd-Chiari syndrome</td>
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<tr>
<td>Congenital hepatic fibrosis</td>
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<tr>
<td>CF</td>
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<td></td>
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<tr>
<td>Autoimmune hepatitis</td>
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<td></td>
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<tr>
<td>Cryptogenic cirrhosis</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Drug induced hepatotoxicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-alcoholic steatohepatitis</td>
<td></td>
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</tr>
</tbody>
</table>

*leading cause in adults; **leading cause in children

Clinical Indications

- early referral for transplant should be considered for all patients with progressive liver disease not responsive to medical therapy, especially:
  - decompensated cirrhosis (ascites, esophageal variceal hemorrhage, spontaneous hepatic encephalopathy, coagulopathy, progressive jaundice, severe fatigue)
  - unresectable primary liver cancers
  - fulminant hepatic failure
  - end-stage liver disease with life expectancy <1 yr and if no other therapy is appropriate

Criteria for Transplantation

- Model for End-Stage Liver Disease (MELD); prognostic model to estimate 3 mo survival and disease severity if patient does not receive transplant; based on creatinine, bilirubin, INR; MELD scores from 6–40 used to prioritize liver allocation
- Child-Turcotte-Pugh Score: classification system to assess the prognosis and mortality of liver disease; patient must have ≥7 points (Class B)

Contraindications

- active alcohol/substance abuse
- extrahepatic malignancy within 5 yr
- advanced cardiopulmonary disease
- active uncontrolled infection

Post-Operative Complications

- primary non-function (graft failure); urgent re-transplantation is indicated
- acute and chronic rejection, ischemia-reperfusion injury
- vascular: hepatic artery or portal vein thrombosis, IVC obstruction
- biliary complications: fever, increasing bilirubin and ALP
- complications related to immunosuppression: HTN, renal disease, DM, obesity, hyperlipidemia, osteoporosis, malignancy, neurologic complications, infection (leading cause of mortality following transplant)

Prognosis

- patient survival at 1 yr: 85%
- graft survival at 1 yr: >80%, at 5 yr: 60-70%
Biliary Tract

Cholelithiasis

Definition
• the formation of gallstones

Pathogenesis
• imbalance of cholesterol and its solubilizing agents (bile salts and lecithin)
• excessive hepatic cholesterol secretion → bile salts and lecithin are “overloaded” → supersaturated cholesterol can precipitate and form gallstones
• North America: cholesterol stones (80%), pigment stones (20%)

Risk Factors
• cholesterol stones
  ▪ obesity, age <50
  ▪ estrogens: female, multiparity, OCPs
  ▪ ethnicity: First Nations heritage (especially Pima Indians) > Caucasian > Black
  ▪ terminal ileal resection or disease (e.g. Crohn’s disease)
  ▪ impaired gallbladder emptying: starvation, TPN, DM
  ▪ rapid weight loss: rapid cholesterol mobilization and biliary stasis
• pigment stones (contain calcium bilirubinate)
  ▪ cirrhosis
  ▪ chronic hemolysis
  ▪ biliary stasis (strictures, dilation, biliary infection)
• protective factors: statins, vitamin C, coffee, exercise

Figure 27. Gallstone disease

Clinical Presentation
• asymptomatic (80%)
  ▪ most do NOT require treatment
  ▪ consider cholecystectomy if: increased risk of malignancy (choledochal cysts, Caroli’s disease, porcelain or calcified gallbladder), sickle cell disease, pediatric patient, bariatric surgery, immunosuppression
• biliary colic (10-25%)
• cholecystitis
• choledocholithiasis (8-15%)
• cholangitis
• gallstone pancreatitis (see Acute Pancreatitis, GS52)
• gallstone ileus (0.3-0.5%)
• other: empyema of the gallbladder, liver abscess, gallbladder perforation with bile peritonitis

Investigations
• Labs
  ▪ CBC, LFTs, amylase, and lipase
U/S: diagnostic procedure of choice
- image for signs of inflammation, obstruction, localization of stones
- 95% specific for detecting stones
- signs: gallbladder wall thickening >4 mm, edema (double-wall sign), gallbladder sludge, pericholecystic fluid, sonographic Murphy's sign
- ERCP
  - visualization of upper GI tract, ampullary region, biliary and pancreatic ducts
  - method for treatment of CBD stones in periampullary region
- complications: traumatic pancreatitis (1-2%), pancreatic or biliary sepsis

MRCP
- same information gained as ERCP but non-invasive
- cannot be used for therapeutic purposes
- PTC
  - injection of contrast via needle passed through hepatic parenchyma
  - useful for proximal bile duct lesions or when ERCP fails or not available
  - requires prophylactic antibiotics
- contraindications: coagulopathy, ascites, peri/intrahepatic sepsis, disease of right lower lung or pleura
- complications: bile peritonitis, chylothorax, pneumothorax, sepsis, hemobilia
- HIDA scan
  - used less commonly
  - radioisotope technetium-99 injected into a vein is excreted in high concentrations into bile, allowing visualization of the biliary tree
  - does not visualize stones; diagnosis by seeing occluded cystic duct or CBD

### Biliary Colic

**Pathogenesis**
- gallstone transiently impacted in cystic duct, no infection

**Clinical Features**
- steady, severe dull pain in epigastrium or RUQ for minutes to hours, crescendo-decrescendo pattern
- may present with chest pain
- N/V
- frequently occurs at night or after fatty meal, not after fasting
- can radiate to right shoulder or scapula
- patients often restless
- no peritoneal findings, no systemic signs

**Investigations**
- normal blood work: CBC, electrolytes, LFTs, bilirubin, amylase
- U/S shows cholelithiasis, may show stone in cystic duct

**Treatment**
- analgesia, rehydration during colic episode
- elective cholecystectomy (95% success)
  - complications: CBD injury (0.3-0.5%), hollow viscus injury, bile peritonitis, vessel injury
  - laparoscopic cholecystectomy is the standard of care, no benefit to delaying surgery
  - risk of open cholecystectomy higher in emergency situations

**Acute Cholecystitis**

**Pathogenesis**
- inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or Hartmann's pouch
- no cholelithiasis in 5-10% (see Acalculous Cholecystitis, GS49)

**Clinical Features**
- often have history of biliary colic
- severe constant (hours to days) epigastric or RUQ pain, anorexia, N/V, low grade fever (<38.5°C)
- focal peritoneal findings: Murphy's sign, palpable, tender gallbladder (in 33%)
- Boas' sign: right subscapular pain

**Investigation**
- blood work: elevated WBC and left shift, mildly elevated bilirubin, AST, ALT, and ALP
- U/S: 98% sensitive, consider HIDA scan if U/S negative

**Complications**
- gallbladder mucocele (hydrops): long-term cystic duct obstruction results in mucous accumulation in gallbladder (clear fluid)
- gangrene (20%), perforation (2%): result in abscess formation or peritonitis
- empyema of gallbladder: suppurative cholecystitis, pus in gallbladder + sick patient
• cholecystoenteric fistula, from repeated attacks of cholecystitis, can lead to gallstone ileus
• emphysematous cholecystitis: bacterial gas present in gallbladder lumen, wall, or pericholecystic space (risk in diabetic patient)
• organisms involved in secondary infection: *E. coli, Klebsiella, Enterococcus*
• Mirizzi syndrome: extra-luminal compression of CBD/CHD due to large stone in cystic duct

**T**reatment
- admit, hydrate, NPO, NGT (if persistent vomiting from associated ileus), analgesics once diagnosis is made
- antibiotics
  - cefazolin if uncomplicated cholecystitis
- cholecystectomy
  - early (within 72 h) vs. delayed (after 6 wk)
    - equal morbidity and mortality
    - early cholecystectomy preferred: shorter hospitalization and recovery time, no benefit to delaying surgery
  - emergent OR indicated if high risk, e.g. emphysematous
    - laparoscopic: reduced risk of wound infections, shorter hospital stay, reduced post-operative pain, increased risk of bile duct injury
- intra-operative cholangiography (IOC)
  - indications: clarify bile duct anatomy, obstructive jaundice, history of biliary pancreatitis, small stones in gallbladder with a wide cystic duct (>15 mm), single faceted stone in gallbladder, bilirubin >137 µmol/L
- percutaneous cholecystostomy tube: critically ill or if general anesthetic contraindicated

## Acalculous Cholecystitis

**Definition**
- acute or chronic cholecystitis in the absence of stones

**Pathogenesis**
- typically due to gallbladder ischemia, stasis

**Risk Factors**
- DM, immunosuppression, ICU admission, trauma patient, TPN, sepsis

**Clinical Features**
- see Acute Cholecystitis, GS48
- occurs in 20% of cases of acute cholecystitis

**Investigations**
- U/S: shows sludge in gallbladder, other U/S features of cholecystitis (see Acute Cholecystitis, GS48)
- CT or HIDA scan

**Treatment**
- broad-spectrum antibiotics, cholecystectomy
- if patient unstable → cholecystostomy

## Choledocholithiasis

**Definition**
- stones in CBD

**Clinical Features**
- 50% asymptomatic
- often have history of biliary colic
- tenderness in RUQ or epigastrium
- acholic stool, dark urine, fluctuating jaundice
- primary vs. secondary stones
  - primary: formed in bile duct, indicates bile duct pathology (e.g. benign biliary stricture, sclerosing cholangitis, choledochal cyst, CF)
  - secondary: formed in gallbladder (85% of cases in U.S.)

**Investigations**
- CBC: usually normal; leukocytosis suggests cholangitis
- LFTs: increased AST, ALT early in disease, increased bilirubin (more sensitive), ALP, GG later
- amylase/lipase: to rule out gallstone pancreatitis
- U/S: intra-/extra-hepatic duct dilatation; differential diagnosis is choledochal cyst
- ERCP, PTC
- MRCP (90% sensitive, almost 100% specific, not therapeutic)
Complications
• cholangitis, pancreatitis, biliary stricture, and biliary cirrhosis

Treatment
• if no evidence of cholangitis: treat with ERCP for CBD stone extraction possibly followed by elective cholecystectomy in 25% of patients

Acute Cholangitis

Pathogenesis
• obstruction of CBD leading to biliary stasis, bacterial overgrowth, suppuration and biliary sepsis — may be life-threatening, especially in elderly

Etiology
• choledocholithiasis (60%), stricture, neoplasm (pancreatic or biliary), extrinsic compression (pancreatic pseudocyst or pancreatitis), instrumentation of bile ducts (PTC, ERCP), biliary stent
• organisms: E. coli, Klebsiella, Pseudomonas, Enterococcus, B. fragilis, Proteus

Clinical Features
• Charcot’s triad: fever, RUQ pain, jaundice
• Reynold’s pentad: fever, RUQ pain, jaundice, shock, confusion
• may have N/V, abdominal distention, ileus, acholic stools, tea-coloured urine (elevated direct bilirubin)

Investigations
• CBC: elevated WBC + left shift
• may have positive blood cultures
• LFTs: obstructive picture (elevated ALP, GGT, and conjugated bilirubin, mild increase in AST, ALT)
• amylase/lipase: rule out pancreatitis
• U/S: intra-/extra-hepatic duct dilatation

Treatment
• initial: NPO, fluid and electrolyte resuscitation, ± NGT, IV antibiotics (treats 80%)
• biliary decompression
  ▪ ERCP + sphincterotomy: diagnostic and therapeutic
  ▪ PTC with catheter drainage: if ERCP not available or unsuccessful
  ▪ laparotomy with CBD exploration and T-tube placement if above fails
• all patients should also have a cholecystectomy, unless contraindicated

Prognosis
• suppurative cholangitis mortality rate: 50%

Gallstone Ileus

Pathogenesis
• repeated inflammation causing a cholecystoenteric fistula (usually duodenal) → large gallstone enters the gut and impacts at or near the ileocecal valve, causing a true bowel obstruction (note: ileus is a misnomer in this context)

Clinical Features
• crampy abdominal pain, N/V (see Large Bowel Obstruction, GS30)

Investigations
• AXR: dilated small intestine, air fluid levels, may reveal radiopaque gallstone, air in biliary tree (pneumobilia) (40%)
• CT: biliary tract air, obstruction, gallstone in intestine
• Rigler’s triad: pneumobilia (air in biliary tree), small bowel obstruction (partial or complete), gallstone (usually in right iliac fossa)

Treatment
• fluid resuscitation, NGT decompression
• surgery: enterolithotomy and removal of stone, inspect small and large bowel for additional proximal stones
• may close fistula surgically or manage expectantly (can resolve spontaneously)
• cholecystectomy either during enterolithotomy or after recovery if patient experiences gallbladder symptoms

Charcot’s Triad
Fever, RUQ pain, jaundice

Reynold’s Pentad
Fever, RUQ pain, jaundice, shock, confusion

Common Bacteria in Biliary Tract
KEEPS
Klebsiella
Enterococcus
E. coli, Enterobacter
Proteus, Pseudomonas
Serratia

Rigler’s Triad of Gallstone Ileus
• Pneumobilia
• Small bowel obstruction
• Gallstone

Bouveret’s Syndrome
Gastric outlet/duodenal obstruction caused by a large gallstone passing through a cholecystogastric or cholecystoduodenal fistula
Carcinoma of the Gallbladder

Risk Factors
- chronic symptomatic gallstones (70% of cases), old age, female, gallbladder polyps, porcelain gallbladder, chronic infection (Salmonella, Helicobacter), abnormal pancreaticobiliary duct junction

Clinical Features
- majority are adenocarcinoma
- may be incidental finding on elective cholecystectomy (~1% of elective cholecystectomies)
- many patients are asymptomatic until late
- local: non-specific RUQ pain, ± palpable RUQ mass
- Courvoisier’s gallbladder: an enlarged, often palpable gallbladder in a patient with carcinoma of the head of the pancreas; associated with jaundice due to obstruction of the CBD
- systemic: jaundice (50%) due to invasion of CBD or compression of CBD by pericholedochal nodes, weight loss, malaise, anorexia
- early local extension to liver, may extend to stomach, duodenum
- early metastasis common to liver, lung, bone

Investigations
- U/S: mural thickening, calcification, loss of interface between gallbladder and liver, fixed mass
- endoscopic U/S (EUS): good for distinguishing carcinomas from other diagnoses such as polyps, good for staging, allows sampling of bile for cytology
- abdominal CT: polypoid mass, mural thickening, liver invasion, nodal involvement, distant metastases
- MRI/MRCP: good for distinguishing benign and malignant polyps

Treatment
- if carcinoma of the gallbladder is suspected pre-operatively, an open cholecystectomy should be considered to avoid tumour seeding of the peritoneal cavity
- confined to mucosa (rare): cholecystectomy
- beyond mucosa: cholecystectomy, en bloc wedge resection of 3-5 cm underlying liver, dissection of hepaticoduodenal lymph nodes

Prognosis
- poor 5 yr survival (10%) as gallbladder carcinoma is often detected late
- better outcomes when detected incidentally following cholecystectomy

Cholangiocarcinoma

Definition
- malignancy of extra- or intrahepatic bile ducts

Risk Factors
- age 50-70, gallstones, ulcerative colitis, primary sclerosing cholangitis, choledochal cyst, Clonorchis sinensis infection (liver fluke), chronic intrahepatic stones (hepatolithiasis)

Clinical Features
- majority are adenocarcinomas
- gradual signs of biliary obstruction: jaundice, pruritus, dark urine, pale stools
- anorexia, weight loss, RUQ pain, Courvoisier’s sign (if CBD obstructed), hepatomegaly
- early metastases are uncommon, but commonly tumour grows into portal vein or hepatic artery
- Klatskin tumour: cholangiocarcinoma located at bifurcation of common hepatic duct

Investigations
- LFTs show obstructive picture
- U/S, CT: bile ducts usually dilated, but not necessarily
- ERCP or PTC: to determine resectability, for biopsies
- CXR, bone scan: for metastatic workup

Treatment
- if resectable: biliary drainage and wide excision margin
  - upper third lesions: duct resection + Roux-en-Y hepaticojejunostomy, ± liver resection
  - middle third lesions (uncommon): duct resection + Roux-en-Y hepaticojejunostomy
  - lower third lesions: Whipple procedure
- unresectable lesions: stent or choledochojejunostomy (surgical bypass)
- chemotherapy ± radiotherapy
- role for transplantation in some patients with Klatskins tumours

Prognosis
- radiotherapy useful for additional palliation, chemotherapy may be helpful
- the more proximal to the liver, the worse the prognosis
- overall 5 yr survival: 15%

Prognosis

Courvoisier’s Sign
Palpable, nontender distended gallbladder due to CBD obstruction. Present in 33% of patients with pancreatic carcinoma. The distended gallbladder could not be due to acute cholecystitis or stone disease because the gallbladder would actually be scarred and smaller, not larger

Efficacy of Neoadjuvant Chemoradiation, Followed by Liver Transplantation, for Perihilar Cholangiocarcinoma at 12 US Centers
Gastroenterology 2012;143:88-96
Purpose: To determine the effectiveness of neoadjuvant chemoradiation and liver transplantation for unresectable perihilar cholangiocarcinoma and to determine the appropriateness of the United Network of Organ Sharing/Organ Procurement and Transportation Network (UNOS/GPRTN) criteria for model of end-stage liver disease (MELD) exception for patients with this disease.
Methods: Study conducted from 1993-2010 in 12 transplant centers. 287 patients included.
Results: Median follow-up was 2.5 yr; 40% of patients (n=112) died after a median of 1.2 yr from presentation, and of these, 65 died pretransplant. Post-transplant, 40 patients had recurrence and 62 died. Recurrence-free survival at 2, 5, and 10 yrs were 76%, 65%, and 56%, respectively. Intention-to-treat survival rates at 2 and 5 yrs were 66% and 53%, respectively. 23% of patients left the waiting list after a median of 4.6 mo. The waiting list drop-out rate increased by an average of 11.5% every 3 mo. Patients who received transplantation outside of the criteria for MELD exception or who had a malignancy within 3 yr had significantly worse recurrence-free survival compared to those who met the criteria (HR=1.59, 95%CI 1.26, 1.95). Recurrence-free survival at 5 yr was shorter for patients with tumours >3 cm (HR=3; p<0.001).
Conclusions: Neoadjuvant chemoradiation and liver transplantation are effective treatments for unresectable perihilar cholangiocarcinoma. Furthermore, the UNOS/GPRTN criteria for MELD exception appear to be appropriate.

Obstructive jaundice is the most common presenting symptom for cholangiocarcinoma

Ranson’s Criteria
A. At admission
1. Age >55 yr
2. WBC >16 x 10^9/L
3. Glucose >11 mmol/L
4. LDH ≥350 IU/L
5. AST ≥250 IU/L
B. During initial 48 h
1. Hct drop >10%
2. BUN rise >1.8 mmol/L
3. Arterial PO2 <60 mmHg
4. Base deficit >4 mmol/L
5. Calcium <2 mmol/L
6. Fluid sequestration >6 L
C. Interpretation
≥2 = difficult course
≥3 = high mortality (>15%)
Pancreas

Acute Pancreatitis

- see Gastroenterology, G44

GALLSTONE PANCREATITIS (35% of Acute Pancreatitis)

Pathogenesis
- obstruction of pancreatic duct by large or small gallstones and biliary sludge
- backup of pancreatic enzymes can cause autodigestion of the pancreas

Clinical Features (Pancreatitis of Any Etiology)
- pain (epigastric pain radiating to back), N/V, ileus, peritoneal signs, jaundice, fever
- Inglefinger's sign: pain worse when supine, better when sitting forward
- rarely may have coexistent cholangitis or pancreatic necrosis
- Ranson's criteria for determining prognosis of acute pancreatitis (see sidebar)
- physical exam may show: tachypnea, tachycardia, hypotension, abdominal distention and tenderness, Cullen's sign, Grey Turner's sign

Investigations
- high amylase (higher than alcoholic pancreatitis), lipase, leukocytosis
- elevated ALT (>150 IU/L), AST strongly suggest gallstone etiology of pancreatitis
- U/S may show multiple stones (may have passed spontaneously), edematous pancreas
- CXR, AXR, CT (if severe to evaluate for complications)

Treatment
- supportive: e.g. NPO, hydration, analgesia, early enteric nutrition
- antibiotics for severe cases of necrotizing pancreatitis or signs of sepsis
- stone often passes spontaneously (~90%); usually no surgical management in uncomplicated acute pancreatitis
- cholecystectomy during same admission (25-60% recurrence if no surgery)
- may need urgent ERCP + sphincterotomy if failure of conservative management if stone impacted in CBD (benefits of early ERCP controversial)
- early ERCP if concomitant cholangitis
- **surgical indications** in acute pancreatitis (rare):
  - debridement and drain placement for necrotizing pancreatitis if refractory to medical management, if septic or in ICU without other sources of sepsis

Complications
- pseudocyst (collection of pancreatic secretions >4 wk old surrounded by a defined wall of granulation tissue)
- abscess/infection, necrosis
- splenic/mesenteric/portal vessel thrombosis or rupture
- pancreatic ascites/pancreatic pleural effusion
- DM
- ARDS/sepsis/multiorgan failure
- coagulopathy/DIC
- encephalopathy
- severe hypocalcemia

Chronic Pancreatitis

- see Gastroenterology, G46

Surgical Treatment
- treatment is generally medical
- indications for surgery
  - failure of medical treatment
  - debilitating abdominal pain
  - pseudocyst complications: persistence, hemorrhage, infection, rupture
  - CBD obstruction (e.g. strictures), duodenal obstruction
  - pancreatic fistula, variceal hemorrhage secondary to splenic vein obstruction
  - rule out pancreatic cancer (present in 15% of chronic pancreatitis treated surgically)
  - anatomical abnormality causing recurrent pancreatitis
- pre-operative CT and/or ERCP are mandatory to delineate anatomy
- minimally invasive options
  - endoscopic pancreatic duct decompression: less effective than surgery
  - extracorporeal shockwave lithotripsy: if pancreatic duct stones
  - celiac plexus block: lasting benefit in 30% patients, less effective in those <45 yr or with prior pancreatic surgery

The hallmark of chronic pancreatitis is epigastric pain radiating to the back
**Surgical Options**
- Drainage procedures: only effective if ductal system is dilated
  - Puestow procedure (lateral pancreaticojejunostomy): improves pain in 80% of patients
  - Pancreatectomy: best option in absence of dilated duct
  - Proximal disease: Whipple procedure (pancreatoduodenectomy) – pain relief in 80%
  - Distal disease: distal pancreatectomy ± Roux-en-Y pancreaticojejunostomy
  - Total pancreatectomy: refractory disease
  - Denervation of celiac ganglion and splanchnic nerves

**Pseudocyst**
- Localized fluid collections rich in pancreatic enzymes, with a non-epithelialized wall consisting of fibrous and granulation tissue
- Complication of chronic and/or acute pancreatitis
- Often resolve spontaneously
- Cyst wall must be mature prior to drainage (4-6 wk)
- Pseudoaneurysm an absolute contraindication to endoscopic drainage, must embolize first

**Treatment**
- Surgical drainage (gold standard)
  - Cystgastrostomy
  - Cystenterostomy
  - Resection
- Endoscopic drainage
  - Cystgastrostomy
  - Cystduodenostomy
  - Percutaneous catheter drainage
- Consider biopsy of cyst wall to rule out cystadenocarcinoma

**Pancreatic Cancer**

**Epidemiology**
- Fourth most common cause of cancer-related mortality in both men and women in Canada
- M:F = 1.3:1, average age: 50-70

**Risk Factors**
- Increased age
- Smoking: 2-5x increased risk, most clearly established risk factor
- High fat/low fibre diets, heavy alcohol use
- Obesity
- DM, chronic pancreatitis
- Partial gastrectomy, cholecystectomy
- Chemicals: betanaphthylamine, benzidine
- African descent

**Clinical Features**
- Head of the pancreas (70%)
  - Weight loss, obstructive jaundice, steatorrhea, vague constant mid-epigastric pain (often worse at night, may radiate to back)
  - Painless jaundice (occurs more often with peri-ampullary), Courvoisier’s sign (see sidebar GS49)
- Body or tail of pancreas (30%)
  - Tends to present later and usually inoperable
  - Weight loss, vague mid-epigastric pain
  - <10% jaundiced
  - Sudden onset DM

**Investigations**
- Serum chemistry is non-specific, can have elevated ALP and bilirubin >300 µmol/L
- CA 19-9 (most useful serum marker of pancreatic cancer)
- U/S, contrast CT (also evaluates metastasis and resectability), ERCP, MRI, MRCP

**Pathology**
- Ductal adenocarcinoma: most common type (75-80%); exocrine pancreas
- Intraductal papillary mucinous neoplasm (IPMN)
- Other: pancreatic neuroendocrine tumours (non-functional, insulinoma, gastrinoma, VIPoma, glucagonoma, somatostatinoma), mucinous cystic neoplasm (MCN), acinar cell carcinoma
- See Surgical Endocrinology, GS61 for functional pancreatic neuroendocrine tumours

**Treatment**
- Resectable (10-20% of pancreatic cancer)
  - No involvement of liver, peritoneum, or vasculature (hepatic artery, SMA, SMV, portal vein, IVC, aorta), no distant metastasis
  - Whipple procedure (pancreatoduodenectomy) for cure <5% mortality
  - Distal pancreatectomy ± splenectomy, lymphadenectomy if carcinoma of midbody and tail of pancreas

**Pancreatic Neuroendocrine Tumours**
- Exocrine pancreas
- Insulinoma
- Gastrinoma
- Glucagonoma
- Somatostatinoma
- See Surgical Endocrinology, GS61 for functional pancreatic neuroendocrine tumours

**Steps of a Whipple Resection**
1. Assessment of metastatic disease (all peritoneal surfaces)
2. Mobilization of the duodenum and head of the pancreas
3. Identification of the superior mesenteric vein and mobilization of the pancreatic neck
4. Mobilization of the stomach; dissection of the hepatoduodenal ligament and cholecystectomy
5. Division of the stomach, proximal jejunum, and CBD
6. Transection of the pancreatic neck and dissection of the uncinate process from the retroperitoneum
7. Restoration of gastrointestinal continuity; construction of a pancreaticojejunostomy, hepatojejunostomy, gastrojejunostomy using a neoduodenum

**Removed**
- CBD
- Gallbladder
- Duodenum
- Pancreatic head
- Distal stomach (sometimes)
- borderline resectable
  - tumours that abut the SMA, SMV, portal vein, hepatic artery, or celiac artery
- non-resectable (palliative → relieve pain, obstruction)
  - most body/tail tumours are not resectable (due to late presentation)
  - relieve biliary/duodenal obstruction with endoscopic stenting or double bypass procedure (choledochoenterostomy + gastroenterostomy)
  - chemotherapy (gemcitabine, folfirinox), radiotherapy – only slightly increase survival

**Prognosis**
- most important prognostic indicators are lymph node status, margin status, size >3 cm, perineural invasion (invasion of tumour into microscopic nerves of pancreas)
- overall 5 yr survival for all patients with pancreas cancer is 1%; following surgical resection 5 yr survival is 20%
- median survival for unresectable disease: 3-6 mo if metastatic, 8-12 mo if locally advanced at presentation

**Table 20. TNM Classification System for Exocrine and Endocrine Tumours of the Pancreas**

<table>
<thead>
<tr>
<th>Primary Tumour (T)</th>
<th>Regional Lymph Nodes (N)</th>
<th>Distant Metastasis (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>NX</td>
<td>M0</td>
</tr>
<tr>
<td>T0</td>
<td>N0</td>
<td>M1</td>
</tr>
<tr>
<td>Tis</td>
<td>N1</td>
<td></td>
</tr>
<tr>
<td>T1</td>
<td>Carcinoma in situ</td>
<td></td>
</tr>
<tr>
<td>T2</td>
<td>Tumour limited to pancreas, &lt;2 cm in greatest dimension</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour extends beyond pancreas, no involvement of celiac axis or SMA</td>
<td></td>
</tr>
<tr>
<td>T4</td>
<td>Tumour involves celiac axis or SMA (unresectable)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 21. Staging and Treatment of Pancreatic Cancer**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Classification</th>
<th>5 Yr Survival</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Tis, N0, M0</td>
<td>14%</td>
<td>Surgical resection ± chemotherapy</td>
</tr>
<tr>
<td>IA</td>
<td>T1, N0, M0</td>
<td>12%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IB</td>
<td>T2, N0, M0</td>
<td>5%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIA</td>
<td>T3, N0, M0</td>
<td>3%</td>
<td>Same as above</td>
</tr>
<tr>
<td>IIB</td>
<td>T4, any N, M0</td>
<td>1%</td>
<td>Borderline resectable, trial of chemotherapy and radiation</td>
</tr>
<tr>
<td>IV</td>
<td>any T, any N, M1</td>
<td>1%</td>
<td>Non-resectable, palliative treatments</td>
</tr>
</tbody>
</table>

**Figure 28. Schematic of Whipple resection, showing the resected components**

**Diagnostic Value of Serum Carbohydrate Antigen 19-9 in Pancreatic Cancer: A Meta-Analysis**

*Summary:* 11 studies with 2,316 patients were included in the analysis. The sensitivity of CA19-9 in the diagnosis of pancreatic cancer was found to be 0.8 (95% CI 0.77-0.82) and the specificity also 80% (95% CI 0.77-0.82) with a diagnostic odds ratio of 14.79 (95% CI 8.55-25.59). Overall, CA19-9 plays an important role in the diagnosis of pancreatic cancer.
Spleen

Splenic Trauma

- typically from blunt trauma (especially in people with splenomegaly)
- most common intra-abdominal organ injury in blunt trauma
- may have Kehr’s sign

Treatment

- non-operative
  - in stable patients: extended bed rest with serial hematocrit levels, close monitoring for 3-5 d; pediatric guidelines for days of bed rest is grade plus 1 (i.e. grade 3 splenic laceration requires 4 d of bed rest)
  - hemostatic control
  - splenic artery embolization if patient stable and one of: active contrast extravasation, splenic pseudoaneurysm, hemoperitoneum
- operative
  - splenorrhaphy (suture of spleen) ± splenic wrapping with hemostatic mesh – if patient hemodynamically stable, patient has stopped bleeding and laceration does not involve hilum
  - partial splenectomy, rarely performed due to risk of recurrent hemorrhage
  - total splenectomy if patient unstable or high-grade injury

Splenectomy

Indications

- splenic trauma (most common reason for splenectomy), hereditary spherocytosis, primary hypersplenism, chronic immune thrombocytopenic purpura (ITP), splenic vein thrombosis causing esophageal varices, splenic abscess, thrombotic thrombocytopenic purpura (TTP), sickle cell disease
- does not benefit all thrombocytopenic states (e.g. infection, most malignancies involving the bone marrow, drugs/toxins)
- probability of cure of ITP by splenectomy is 60-70%, may be predicted by response to IVIg

Complications

- short-term
  - injury to surrounding structures (e.g. gastric wall, tail of pancreas)
  - post-operative thrombocytosis, leukocytosis
  - thrombosis of portal, splenic, or mesenteric veins
  - subphrenic abscess
- long-term
  - post-splenectomy sepsis (encapsulated organisms): 4% of splenectomized patients (highest risk in those <16 yr old)
    - 50% mortality
    - prophylaxis with vaccinations, ideally 2 wk pre- or post-operative (pneumococcal, H. influenzae, and meningococcus)
    - liberal use of penicillin especially in children <6 yr old
  - splenosis: intra-abdominal “seeding” of splenic tissue during removal
Benign Breast Lesions

Three Categories
1. nonproliferative
2. proliferative without atypia
3. atypical hyperplasia

NONPROLIFERATIVE LESIONS
- benign breast condition characterized by fibrous and cystic changes in the breast
- most common: breast cysts
- other lesions include papillary apocrine change, epithelial-related calcifications and mild hyperplasia of the usual type
- no increased risk of breast cancer
- age 30 to menopause (and after if HRT used)
- clinical features
  - breast pain, focal areas of nodularity or cysts often in the upper outer quadrant, frequently bilateral, mobile, varies with menstrual cycle, nipple discharge (straw-like, brown, or green)
- treatment
  - evaluation of breast mass (U/S, mammography as indicated) and reassurance
  - no strong evidence for avoidance of xanthine-containing products (coffee, tea, chocolate, cola)
  - analgesia (ibuprofen, ASA)
  - for severe symptoms: OCP, danazol, bromocriptine

Malignant
- Breast cancer (likely invasive, DCIS rarely forms a breast mass)
- Malignant phyllodes
- Angiosarcoma (rare)
### Proliferative Lesions – without Atypia

<table>
<thead>
<tr>
<th>Table 22. Proliferative Lesions - without Atypia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical Features</td>
</tr>
<tr>
<td>-------------------</td>
</tr>
<tr>
<td><strong>Fibroadenoma</strong></td>
</tr>
<tr>
<td><strong>Intraductal Papilloma</strong></td>
</tr>
<tr>
<td><strong>Usual Ductal Hyperplasia</strong></td>
</tr>
<tr>
<td><strong>Sclerosing Adenosis</strong></td>
</tr>
</tbody>
</table>

### Atypical Hyperplasia
- can involve ducts (ductal hyperplasia with atypia) or lobules (lobular hyperplasia with atypia)
- cells lose apical-basal orientation
- increased risk of breast cancer
- diagnosis: core or excisional biopsy
- treatment: complete resection, risk modification (avoid exogenous hormones), close follow-up

### Other Lesions

#### Fat Necrosis
- uncommon, result of trauma (may be minor, positive history in only 50%), after breast surgery (i.e. reduction)
- firm, ill-defined mass with skin or nipple retraction, ± tenderness
- regress spontaneously, but complete imaging ± biopsy to rule out carcinoma

#### Mammary Duct Ectasia
- obstruction of a subareolar duct leading to duct dilation, inflammation, and fibrosis
- may present with nipple discharge, bluish mass under nipple, local pain
- risk of secondary infection (abscess, mastitis)
- resolves spontaneously

#### Montgomery Tubercle
- Montgomery tubercles (or Morgagni tubercles) are papular projections at the edge of the areola
- obstruction of these glands can lead to inflammation or cystic collections (cyst of Montgomery i.e. retroareolar cyst)
- if signs of secondary infection, start treatment for mastitis
- resolves spontaneously in weeks to years

#### Abscess
- lactational (see Obstetrics, OB48) vs. periductal/subareolar
- unilateral localized pain, tenderness, erythema, subareolar mass, nipple discharge, nipple inversion
- rule out inflammatory carcinoma, as indicated
- treatment: initially broad-spectrum antibiotics and I&D, if persistent total duct excision (definitive)
- if mass does not resolve: U/S to assess for presence of abscess, core biopsy to exclude cancer, consider MRI
Breast Cancer

Epidemiology
- leading cancer diagnosis in women in NA, 2nd leading cause of cancer mortality in women
- 1/8 (12.8% lifetime risk) women in Canada will be diagnosed with breast cancer in their lifetime
- 1/30 women in Canada will die from breast cancer

Risk Factors
- gender (99% female)
- age (80% >40 yr old)
- personal history of breast cancer and/or prior breast biopsy (regardless of pathology)
- family history of breast cancer (greater risk if relative was first degree and premenopausal)
- high breast density, nulliparity, first pregnancy >30 yr, menarche <12 yr, menopause >55 yr
- decreased risk with lactation, early menopause, early childbirth
- radiation exposure (e.g. mantle radiation for Hodgkin's disease)
- >5 yr HRT use, >10 yr OCP use
- BRCA1 and BRCA2 gene mutations
- alcohol use, obesity, sedentary lifestyle

Male breast cancer (<1%)
- most commonly invasive ductal carcinoma
- often diagnosed at later stages
- stage-for-stage similar prognosis to breast cancer in females
- consider genetic testing: most often hormone receptor positive

Investigations
- mammography
  - indications
  - findings indicative of higher risk of malignancy
  - mass that is poorly defined, spiculated border
  - microcalcifications
  - architectural distortion
  - interval mammographic changes
  - normal mammogram does not rule out suspicion of cancer based on clinical findings
- other radiographic studies
  - U/S: differentiate between cystic and solid
  - MRI: high sensitivity, low specificity
  - galactogram/ductogram (for nipple discharge): identifies lesions in ducts
  - metastatic workup indicated in Stage II-IV disease: bone scan, abdominal U/S, CXR (or CT chest/abdomen/pelvis), CT head (if specific neurological symptoms)

Diagnostic Procedures
- needle aspiration: for palpable cystic lesions; send fluid for cytology if blood or cyst does not completely resolve
- U/S or mammography guided core needle biopsy (most common)
- fine needle aspiration (FNA): for palpable solid masses; need experienced practitioner for adequate sampling
- excisional biopsy: only performed as second choice to core needle biopsy; should not be done for diagnosis if possible

Genetic Screening
- consider testing for BRCA1/2 if
  - patient diagnosed with breast AND ovarian cancer
  - strong family history of breast/ovarian cancer
  - family history of male breast cancer
  - young patient (<35 yr)
  - bilateral breast cancer in patients <50 yr

Staging
- patients are assigned a clinical stage pre-operatively (cTNM); following surgery the pathologic stage is determined (pTNM)
- clinical
  - tumour size by palpation, mammogram, U/S and/or MRI
  - nodal involvement by palpation, imaging
  - metastasis by physical exam, CXR, and abdominal U/S (or CT chest/abdomen/pelvis), bone scan (usually done post-operative if node-positive disease)
- pathological
  - tumour size and type (see Pathology below)
  - grade: modified Bloom and Richardson score (I to III) – histologic, nuclear, and mitotic grade
- number of axillary nodes positive for malignancy out of total nodes resected, extranodal extension, sentinel lymph node biopsy (SLNB) positive/negative
- tumour biology: estrogen receptor (ER), progesterone receptor (PR) and HER2/neu oncogene status
- margins: for invasive breast cancer negative margin is sufficient, for DCIS prefer 2mm margin
- lymphovascular invasion (LVI)
- extensive in situ component (EIC): DCIS in surrounding tissue
- involvement of dermal lymphatics (inflammatory) – automatically Stage IIIb

### Table 23. Staging of Breast Cancer (American Joint Committee on Cancer)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumour</th>
<th>Nodes (regional) (clinical)</th>
<th>Metastasis</th>
<th>Survival (5 yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>in situ</td>
<td>None</td>
<td>None</td>
<td>99%</td>
</tr>
<tr>
<td>I</td>
<td>&lt;2 cm</td>
<td>None</td>
<td>None</td>
<td>94%</td>
</tr>
<tr>
<td>II A</td>
<td>&lt;2 cm</td>
<td>Mobile ipsilateral</td>
<td>None</td>
<td>85%</td>
</tr>
<tr>
<td>II B</td>
<td>2-5 cm</td>
<td>None or mobile ipsilateral</td>
<td>None</td>
<td>70%</td>
</tr>
<tr>
<td>II B</td>
<td>or &gt;5 cm</td>
<td>None or mobile ipsilateral</td>
<td>None</td>
<td>70%</td>
</tr>
<tr>
<td>III A</td>
<td>Any size</td>
<td>Fixed ipsilateral or internal mammary</td>
<td>None</td>
<td>52%</td>
</tr>
<tr>
<td>III B</td>
<td>Skin/chest wall invasion</td>
<td>Any</td>
<td>None</td>
<td>48%</td>
</tr>
<tr>
<td>III C</td>
<td>Any size</td>
<td>I ipsilateral infraclavicular/internal mammary plus axillary nodes; ipsilateral supraclavicular node(s) = axillary nodes</td>
<td>None</td>
<td>33%</td>
</tr>
<tr>
<td>IV</td>
<td>Any</td>
<td>Any</td>
<td>Distant</td>
<td>18%</td>
</tr>
</tbody>
</table>

### Pathology

#### NON-INVASIVE

**Ductal Carcinoma in situ (DCIS)**
- proliferation of malignant ductal epithelial cells completely contained within breast ducts, often multifocal
- 80% non-palpable, detected by screening mammogram
- risk of invasive ductal carcinoma in same breast up to 35% in 10 yr
- treatment
  - lumpectomy with wide excision margins + radiation (5-10% risk invasive cancer)
  - mastectomy if large area of disease, high grade, or multifocal (risk of invasive cancer reduced to 1%)
  - possibly tamoxifen as an adjuvant treatment
  - 99% 5 yr survival

**Lobular Carcinoma in situ (LCIS)**
- neoplastic cells completely contained within breast lobule
- no palpable mass, no mammographic findings, usually incidental finding on breast biopsy for another indication
- LCIS is a risk factor for invasive carcinoma (approximately 1%/yr)
- treatment
  - if diagnosed on core biopsy, excisional biopsy necessary to rule out malignancy
  - if diagnosed on excisional biopsy, wide excision not needed since LCIS if often multicentric and not managed as precursor lesion
  - clinical follow-up and surveillance
  - consider chemoprevention (e.g. tamoxifen)

### INVASIVE

**Invasive Ductal Carcinoma (most common 80%)**
- originates from ductal epithelium and infiltrates supporting stroma
- characteristics: hard, scirrhous, infiltrating tentacles, gritty on cross-section

**Invasive Lobular Carcinoma (8-15%)**
- originates from lobular epithelium
- 20% bilateral (i.e. more often than infiltrating ductal carcinoma)
- does not form microcalcifications, harder to detect mammographically (may benefit from MRI)

**Paget’s Disease (1-3%)**
- ductal carcinoma that invades nipple with scaling, eczematoid lesion

**Favourable Features**
- <2 cm
- Grade I (low grade)
- Node negative
- ER positive
- Mucinous pattern
- Inflammatory cancer
- Her2Neu-positive
- Positive margins
- LVI
- ER
- HER2 status and proliferation assessment

**Unfavourable Features**
- >5 cm
- Grade II (high grade)
- Node positive
- ER negative
- Inflammatory cancer
- Her2Neu-positive
- Positive margins
- LVI
- ER
- HER2 status and proliferation assessment
- More painful procedure.

**FNAC**
- Variable sensitivity (35-95%) and specificity (48-100%).
- Quality correlates with skill of aspirator.
- Lower success rates for diagnosis of malignancy for palpable lesions (70%), non-palpable lesions (47%), and lesions <10 mm (60%).
- More accurate for histologic and immunohistochemistry examinations, and differentiation between in situ and invasive malignancies.
- Reliable for testing of ER, PR, and HER2 status and proliferation assessment.
- More painful procedure.

**CNB**
- High sensitivity (95-100%) and specificity (85-100%).
- High success rates for diagnosis of malignancy for palpable lesions (91%), non-palpable lesions (94%), and lesions <10 mm (90%).
- More accurate for histologic and immunohistochemistry examinations, and differentiation between in situ and invasive malignancies.
- Reliable for testing of ER, PR, and HER2 status and proliferation assessment.
- More painful procedure.

**Conclusions:** FNAC is preferable for palpable, low malignancy-risk lesions. However, for potential malignancies, CNB is advantageous with respect to prognosis and prediction and is likely cost-effective in the long-term.
Inflammatory Carcinoma (1-4%)
- ductal carcinoma that invades dermal lymphatics
- most aggressive form of breast cancer
- clinical features: erythema, skin edema, warm, swollen, and tender breast ± lump
- peau d'orange indicates advanced disease (IIIb-IV)

Sarcomas: rare
- most commonly Phyllodes tumour, a variant of fibroadenoma with potential for malignancy
- can also be angiosarcomas – after previous radiation

Lymphoma: rare

Other
- papillary, medullary, mucinous, tubular cancers
- generally better prognosis

Treatment

Table 24. Breast Cancer Treatment by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Primary Treatment Options</th>
<th>Adjuvant Systemic Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 (in situ)</td>
<td>BCS + radiotherapy if margins &gt;1 cm and low nuclear grade Mastectomy* ± SLNB</td>
<td>Consider post-operative tamoxifen for ER+, trastuzumab for HER2+</td>
</tr>
<tr>
<td>I</td>
<td>BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SNB</td>
<td>May not be needed; discuss risks/benefits of chemotherapy and tamoxifen</td>
</tr>
<tr>
<td>II</td>
<td>BCS + axillary node dissection + radiotherapy Mastectomy* + axillary node dissection/SNB</td>
<td>Chemotherapy for premenopausal women or postmenopausal and estrogen receptor (ER) negative, followed by tamoxifen if ER positive</td>
</tr>
<tr>
<td>III</td>
<td>Likely mastectomy + axillary node dissection + radiotherapy after chemotherapy (neoadjuvant)</td>
<td>Neoadjuvant therapy should be considered i.e. pre-operative especially if not resectable chemotherapy and/or hormone therapy. Adjuvant radiation and chemotherapy may also be appropriate (i.e. post-operative)</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Mastectomy + axillary node dissection + radiotherapy</td>
<td>Neoadjuvant therapy</td>
</tr>
<tr>
<td>IV</td>
<td>Surgery as appropriate for local control</td>
<td>Primary treatment is systemic therapy i.e. chemotherapy and/or hormone therapy</td>
</tr>
</tbody>
</table>

BCS = breast conserving surgery; SLNB = sentinel lymph node biopsy
*If no reason to select mastectomy, the choice between BCS + radiotherapy and mastectomy can be made according to patient’s preference since choice of local treatment does not significantly affect survival if local control is achieved

Analysis of Circulating Tumour DNA to Monitor Metastatic Breast Cancer
NEJM 2013;368:1199-1209

Study: The quantification of circulating tumour DNA, cancer antigen 15-3 (CA 15-3), and circulating tumour cells in 30 women with metastatic breast cancer receiving systemic therapy. The results were compared with radiographic imaging of tumours.

Results/Conclusions: Circulating tumour DNA was detected in 97% of women and showed greater correlation with changes in tumour burden than did CA 15-3 or circulating tumour cells, providing the earliest measure of treatment response in 53% of women. CA 15-3 and circulating tumour cells were detected in 76% and 87% of women, respectively. Circulating tumour DNA may therefore be an informative biomarker for metastatic breast cancer.

There is no survival benefit of mastectomy over lumpectomy plus radiation for stage I/II disease

Breast conserving surgery can be offered to most women with stage I/II disease

Primary Surgical Treatment

Breast Conservation Surgery (BCS)
- lumpectomy must be combined with radiation for survival equivalent to mastectomy
- contraindications include
  - high risk of local recurrence e.g. extensive malignant-type calcifications on mammogram, multifocal primary tumours
  - failure to obtain tumour-free margins after re-excision
  - not candidate for radiation therapy (pregnancy, previous radiation, collagen vascular disease)
  - large tumour size relative to breast

Mastectomy
- radical mastectomy (rarely): removes all breast tissue, skin, pectoralis muscle, axillary nodes
- modified radical mastectomy (MRM): removes all breast tissue, skin, and axillary nodes
- simple mastectomy: removes all breast tissue and skin
- see Plastic Surgery, PL33 for breast reconstruction

Sentinel Lymph Node Biopsy (SLNB)
- perform in women with clinically node-negative invasive breast cancer and those with extensive DCIS who are undergoing mastectomy
- patients with clinically suspicious nodes should U/S + FNA prior to decision to proceed with SLNB
- technetium-99 ± blue dye injected at tumour site prior to surgery to identify sentinel node(s)
- intra-operative frozen section evaluated can be considered
- proceed with ALND if >3 positive nodes, with 1-3 nodes whole breast radiation therapy may be alternative
- 5% false negative rate

Axillary Lymph Node Dissection (ALND)
- perform in all patients with pathologic confirmation of nodal involvement (including positive SLNB as above)
- risk of arm lymphedema (10-15%) especially if getting radiation therapy, decreased arm sensation, shoulder pain
ADJUVANT/NEOADJUVANT

Radiation
- indications
  - decrease risk of local recurrence; almost always used after BCS, sometimes after mastectomy
  - inoperable locally advanced cancer
  - axillary nodal radiation may be added if nodal involvement

Hormonal
- indications
  - ER positive plus node-positive or high-risk node-negative
  - SERM if premenopausal (e.g. tamoxifen) or aromatase inhibitors if postmenopausal (e.g. anastrozole); optimal duration 5-10 yr
  - ovarian ablation (e.g. goserelin/GnRH agonist, oophorectomy), progestins (e.g. megestrol acetate), androgens (e.g. fluoxymesterone) are other options
  - palliation for metastatic disease

Chemotherapy
- indications
  - ER negative plus node-positive or high-risk node-negative
  - ER positive and young age
  - stage I disease at high risk of recurrence (high grade, lymphovascular invasion)
  - palliation for metastatic disease
  - can consider oncoftype DX (21 gene analysis) to provide recurrence score (low, intermediate, high)

FOLLOW-UP

Post-Treatment Follow-Up
- assessment and physical exam q3-6mo x 3 yr, q6-12mo x 2yr, and annually thereafter
- following BCS mammography q6-12mo; can reduce to annual once stable, no other routine imaging unless clinically indicated
- women who receive tamoxifen should have regular gynecologic follow-up (increased risk of endometrial cancer)
- psychosocial support and counselling
- delayed breast reconstruction if underwent a mastectomy

Local/Regional Recurrence
- recurrence in treated breast or ipsilateral axilla
- 1% per yr up to maximum of 15% risk of developing contralateral malignancy
- 5x increased risk of developing metastases

Metastasis
- bone > lungs > pleura > liver > brain
- treatment is palliative: hormone therapy, chemotherapy, radiation
- overall survival of metastatic breast cancer is 36-60 mo

Surgical Endocrinology

Thyroid and Parathyroid
- see Endocrinology, E20 and Otolaryngology, OT35

Thyroidectomy
- indications: thyroid cancer, symptomatic thyroid mass or goitre, medically refractory Graves’ or hyperthyroidism
- contraindications: uncontrolled severe hyperthyroidism (i.e. Graves’) due to risk of intra-operative or post-operative thyroid storm
- pre-operative workup: thyroid U/S for thyroid nodules, FNA for large nodules, U/S of the neck for lesions suspicious for papillary or medullary thyroid cancer, CT neck useful to rule out extension, vocal cord function
- complications: hypocalcemia secondary to hypoparathyroidism, recurrent/superior laryngeal nerve injury, neck hematoma, infection, thyrotoxic storm

Parathyroidectomy
- indications: symptomatic primary hyperparathyroidism due to effects of PTH on bone or kidneys, asymptomatic primary hyperparathyroidism with specific laboratory criteria (elevated serum Ca, marked hypercalciuria, Cr clearance <30% normal, bone density reduction with T score <2.5, <50 yr)
- contraindications: familial hypocalciuric hypercalcemia
- pre-operative workup: 99mTc sestamibi scanning, ± SPECT or CT, U/S
- complications: recurrent/superior laryngeal nerve injury, post-operative hypocalcemia, infection, bleeding
Adrenal Gland

- see Endocrinology, E29
- functional anatomy
  - cortex: glomerulosa (mineralocorticoids), fasciculata (glucocorticoids), reticularis (sex steroids)
  - medulla: catecholamines (epinephrine, norepinephrine)
- types of adrenal tumours: functional (e.g. Cushing's syndrome, Conn's syndrome) or non-functional

INTEGRALOMA
- adrenal mass discovered by investigation of unrelated symptoms

Epidemiology
- benign adenoma (38%) > metastases to adrenal (22%) >> cyst, carcinoma, pheochromocytoma, neuroblastoma
- metastasis to adrenal gland from: lung > breast, colon, lymphoma, melanoma, kidney
- peak incidence of carcinoma: females age 50-60, risk decreases with increasing age and male gender

Investigations
- MRI, CT: size >6 cm is best predictor of primary adrenal carcinoma (92% are >6 cm)
- functional studies
  - pheochromocytoma: 24 h urine epinephrine, norepinephrine, metanephrine, normetanephrine, VMA (vanillylmandelic acid)
  - Cushing's: 24 h urine cortisol or 1 mg overnight dexamethasone suppression test
  - aldosteronoma: electrolytes, aldosterone:renin level, saline suppression test if appropriate
  - adrenal androgens: 17-ÖH progesterone, DHEAS
- FNA biopsy: if suspect metastasis to adrenal (must exclude pheochromocytoma first to prevent a hypertensive crisis)
  - indicated if history of cancer or patient is smoker
- iodocholesterol scintigraphy: may distinguish benign vs. malignant disease

Treatment
- functional tumour: resect
- non-functional tumour
  - >4 cm: resect
  - <4 cm: follow-up imaging in 6-12 mo, resect if >1 cm enlargement

Pancreas

INSULINOMA
- tumour that secretes insulin
- most common pancreatic endocrine neoplasm; 10% associated with MEN1 syndrome

Clinical Features
- Whipple's triad
- palpitations, trembling, diaphoresis, confusion, seizure, personality changes

Investigations
- blood work: decreased serum glucose and increased serum insulin and C-peptide
- U/S, CT: insulinomas evenly distributed throughout head, body, tail of pancreas

Treatment
- only 10% are malignant
- enucleation of solitary insulinomas may be done endoscopically
- tumours >2 cm located close to the pancreatic duct may require pancreatectomy or pancreaticoduodenectomy

GASTRINOMA
- tumour secreting gastrin; cause of Zollinger-Ellison syndrome

Clinical Features
- abdominal pain, PUD, severe esophagitis
- multiple ulcers in atypical locations refractory of antacid therapy
Investigations
• blood work: serum gastrin levels (usually >1,000 pg/mL), secretin stimulation test
• U/S, CT: 70-90% found in Passaro’s triangle (head of pancreas medially, 2nd portion of duodenum inferiorly, and the confluence of the cystic and CBD superiorly)
• octreotide scintigraphy scan

Treatment
• 50% are malignant
• surgical resection of tumour dependent on location
• non-surgical treatment: chemotherapy, somatostatin analogues, interferon, chemoembolization
• if inoperable, vagotomy can be performed for symptomatic control

VASOACTIVE INTESTINAL PEPTIDE-SECRETING TUMOUR
• tumour secreting VIP; commonly located in the distal pancreas and most are malignant when diagnosed

Clinical Features
• severe watery diarrhea causing dehydration, weakness, electrolyte imbalance

Investigations
• blood work: serum VIP levels
• U/S, CT

Treatment
• somatostatin analogues
• surgical resection/palliative debulking

Pediatric Surgery

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrocele (see Urology, U29)</td>
<td>1-2% of live births Present at birth, majority close spontaneously by 1 yr M:F = 6:1 Prematurity</td>
<td>Communicating hydroceles: processus vaginalis fails to close with small opening for fluid to move freely between peritoneal cavity through patent processus (if opening progresses to allow passage of intestine, it is a hernia)</td>
<td>Painless scrotal mass Communicating hydroceles increase in size with standing or Valsalva, may be absent in the morning and large in the evening</td>
<td>Transillumination suggests hydrocele Silk glove sign: gently palpating hydrocele sac over pubic tubercle feels like rubbing silk on silk</td>
<td>U/S if suspect pathology</td>
<td>Most resolve spontaneously by 1 yr Surgical repair if: – Persistence &gt;2 yr – Pain – Fluctuating in size which suggests communication – Cosmetic reasons – Infection</td>
<td>&lt;2% recurrence</td>
</tr>
<tr>
<td>Hypertrophic Pyloric Stenosis</td>
<td>0.03-1.0% of live births Can present at 1-20 wk, most commonly at 6-8 wk M:F = 4:1 Early erythromycin exposure (&lt;13 d old)</td>
<td>Acquired pyloric circular muscle hypertrophy results in gastric outlet obstruction Hypovolemia caused by emesis of gastric contents causes hypochloremic hypokalemic metabolic alkalosis Electrolyte exchange based volume retention in kidneys results in paradoxical aciduria</td>
<td>Projectile non-bilious vomiting Vomiting 30-60 min after feeds Hungry after vomiting Dehydration (variable severity) Smooth oblong 1-2 cm mass palpable above umbilicus, “olive” Visible left-to-right gastric contraction “waves” after feeding</td>
<td>Electrolytes (assess hypochloremia, dehydration) U/S shows pyloric length &gt;14 mm, muscle thickness &gt;4 mm Upper GI series necessary only when U/S unavailable or non-diagnostic will show “string sign”</td>
<td>Fluid resuscitate with normal saline, correct electrolyte and acid/base abnormalities with D5, 1/2NS + 20 mEq/L KCl at maintenance rate NGT decompression unnecessary Pyloromyotomy, open (Ramsdell vs. transumbilical or laparoscopic approach) Alternative therapies such as TPN/wait or atropine impractical due to long time course of effect</td>
<td>Pyloromyotomy curative</td>
<td></td>
</tr>
</tbody>
</table>
Table 25. Pediatric Surgery (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Epidemiology and Risk Factors</th>
<th>Pathophysiology</th>
<th>Clinical Features and History</th>
<th>Physical Exam</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Congenital Diaphragmatic Hernias</strong>&lt;br&gt;3 types:&lt;br&gt;- Posterior lateral (Bochdalek)&lt;br&gt;- Left-sided, 95%&lt;br&gt;- Right-sided, 13%&lt;br&gt;- Bilateral, rare, often fatal&lt;br&gt;- Anterior&lt;br&gt;- Morgagni&lt;br&gt;- Hiatus</td>
<td>1 in 2,000 to 5,000 live births&lt;br&gt;Prepresents within hours of life although some cases of delayed presentation&lt;br&gt;M/F = F &gt; 10% are associated with other congenital anomalies&lt;br&gt;Prenatal diagnosis common</td>
<td>Left-sided: small bowel, large bowel, stomach, and solid viscera (spleen, left lobe of liver) herniate into thorax&lt;br&gt;Right-sided: liver, large bowel herniate into thorax</td>
<td>Pulmonary hypoplasia&lt;br&gt;Pulmonary HTN</td>
<td>Decreased air entry&lt;br&gt;± bowel sounds in the chest&lt;br&gt;Displaced heart sounds</td>
<td>Prenatal US/MRI&lt;br&gt;ABG&lt;br&gt;CXR (bowel loops in hemithorax, shifted heart)&lt;br&gt;Echocardiography&lt;br&gt;Genetic consultation if warranted</td>
<td>NGT decompression&lt;br&gt;IV fluids&lt;br&gt;IV antibiotics&lt;br&gt;Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo</td>
<td>&gt;90% survival rate&lt;br&gt;40-70% survival rate&lt;br&gt;Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles</td>
</tr>
<tr>
<td><strong>Meckel’s Diverticulum</strong>&lt;br&gt;Most common remnant of vitelline duct that connects yolk sac with primitive midgut</td>
<td>1-3% of population&lt;br&gt;M/F = 3:1&lt;br&gt;Present most frequently during first 5 yr of life&lt;br&gt;Symptomatic in 2% of cases</td>
<td>Failure of vitelline duct to regress 5-7 wk in utero; 50% contain heterotopic tissue (e.g. gastric mucosa, ectopic pancreas); other associated anomalies include omphalomesenteric fistula, umbilical sinus, umbilical cyst, fibrous band</td>
<td>No specific environmental factor identified&lt;br&gt;Defect in embryogenesis unclear</td>
<td>Bilius esimes is THE cardinal sign, especially if abdomen nondistended&lt;br&gt;If bilious emesis in ill child with distended abdomen, consider surgical exploration to rule out volvulus&lt;br&gt;Rectal bleed (late/omnious signs)&lt;br&gt;Intestinal symptoms</td>
<td>ARX&lt;br&gt;Mickel scan: scan for ectopic gastric mucosa with technetium Tc99m pertechnetate IV (sensitivity 85%, specificity 95%)&lt;br&gt;U/S: “whirlpool” sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies</td>
<td>IV antibiotics&lt;br&gt;Fluid resuscitation&lt;br&gt;EMERGENT LAPAROTOMY&lt;br&gt;Ladd procedure: counterclockwise reduction of midgut volvulus, division of Ladd’s bands, division of peritoneal attachments between cecum and abdominal wall that obstruct duodenum, broadening of the mesentery (open folded mesentery like a book and divide congenital adhesions), ± appendectomy&lt;br&gt;Positioning the bowel into non-rotation (small bowel in right abdomen, large bowel in left abdomen)</td>
<td>Mortality related to length of bowel loss: 10% necrosis — 100% survival rate, 75% necrosis — 35% survival rate&lt;br&gt;Recurrence 2-6%</td>
</tr>
<tr>
<td><strong>Malrotation</strong></td>
<td>1:500 live births&lt;br&gt;1/3 present by 1 wk of age, 3/4 by 1 yr of age&lt;br&gt;M/F = 1:1; higher incidence among patients with cardiac anomalies, heterotaxy syndromes</td>
<td>Failure of gut to normally rotate around SMA with associated abnormal intestinal attachments and anatomic positions&lt;br&gt;Represent a spectrum of rotational abnormalities including complete non-rotation (which is not at high risk for volvulus)</td>
<td>Bilius esimes is THE cardinal sign, especially if abdomen nondistended&lt;br&gt;If bilious emesis in ill child with distended abdomen, consider surgical exploration to rule out volvulus&lt;br&gt;Rectal bleed (late/omnious signs)&lt;br&gt;Intestinal symptoms</td>
<td>ARX: obstruction of proximal small bowel, double-bubble sign, intestinal wall thickened&lt;br&gt;Immediate UGI-dilated duodenum, duodenojejunal segment (ligament of Treitz) right of midline and not fixed posteriorly over spinal column, “corkscrew” sign indicating volvulus&lt;br&gt;U/S: “whirlpool” sign, abnormal SMA/SMV relationship indicates UGI to rule out rotational anomalies</td>
<td>NGT decompression&lt;br&gt;IV fluids&lt;br&gt;IV antibiotics&lt;br&gt;Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo&lt;br&gt;May have bowel dysmotility requiring motility medications</td>
<td>Intubate&lt;br&gt;Orogastric suction&lt;br&gt;Period of respiratory stabilization due to associated pulmonary hypoplasia (may require extrafoetal membrane oxygenation)&lt;br&gt;Surgical repair after stable by hemia reduction and closure of diaphragmatic defect — open vs. thoracoscopic vs. laparoscopic with or without prosthetic or muscular patch depending on size of defect</td>
<td>Later presentations have better outcomes&lt;br&gt;Hearing deficit (40%)&lt;br&gt;Associated GERD&lt;br&gt;MSK defects — chest wall and scoliotic defects a potential complication of thoracotomy&lt;br&gt;Need for long-term surveillance for potential recurrence&lt;br&gt;Failure to thrive&lt;br&gt;Congenital diaphragmatic hernia&lt;br&gt;Chronic lung disease if severe hypoplasia</td>
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<td><strong>Gastroscisis</strong></td>
<td>1:2,000 live births&lt;br&gt;Antenatal diagnosis common&lt;br&gt;Increases with younger maternal age and associated with IUGR&lt;br&gt;M/F = 1:1</td>
<td>Defect of abdominal wall with free extrusion of intestine into amniotic cavity&lt;br&gt;No specific environmental factor identified&lt;br&gt;Defect in embryogenesis unclear</td>
<td>Not associated with genetic syndromes 10% with intestinal atresia&lt;br&gt;Some cases associated with short bowel syndrome due to antenatal volvulus and necrosis of herniated bowel</td>
<td>Hollow viscera (stomach, small and large bowels)&lt;br&gt;Defect lateral to cord (usually right)&lt;br&gt;Bowel may be inflamed, thickened, matted, foreshortened&lt;br&gt;Defect size variable</td>
<td>Prenatal US&lt;br&gt;Elevated MS-AFP&lt;br&gt;NGT decompression&lt;br&gt;IV fluids&lt;br&gt;IV antibiotics&lt;br&gt;Keep viscera moist and protected until surgical reduction with primary abdominal closure or staged closure with silo&lt;br&gt;May have bowel dysmotility requiring motility medications</td>
<td>Mortality related to length of bowel loss: 10% necrosis — 100% survival rate, 75% necrosis — 35% survival rate&lt;br&gt;Recurrence 2-6%</td>
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<td><strong>Omphalocele</strong></td>
<td>1:5,000 live birth&lt;br&gt;Antenatal diagnosis common&lt;br&gt;Lower gestational age&lt;br&gt;Increased maternal age&lt;br&gt;M/F = 1:5.1</td>
<td>Defect of abdominal wall, with extrusion of sac covered viscera (ammon, Wharton’s jelly, peritoneum)&lt;br&gt;Duhamel’s theory – failure of body wall morphogenesis</td>
<td>Associated with genetic syndromes 33-70% (e.g. Pendley’s&lt;br&gt;Cantrell, congenital heart disease, Beckwith-Wiedemann syndrome)&lt;br&gt;Associated pulmonary hypoplasia</td>
<td>Hollow viscera (stomach, small and large bowels, often liver)&lt;br&gt;Cord on the sac</td>
<td>Prenatal US&lt;br&gt;Elevated MS-AFP&lt;br&gt;NGT decompression&lt;br&gt;IV fluids&lt;br&gt;IV antibiotics&lt;br&gt;Small defect (&lt;2 cm): Primary closure&lt;br&gt;Medium (2-4 cm) and large (&gt;4 cm) defects best treated with silver sulfadiazine to promote epithelialization coupled with compression dressing to allow gradual reduction, followed by future repair with or without mesh</td>
<td>&gt;40-70% survival rate&lt;br&gt;Higher survival rates most likely related to antenatal mortality of fetuses with giant omphaloceles</td>
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<td><strong>Umbilical Hernias</strong></td>
<td>Incidence 2-14% Increases with prematurity Decreases with increasing age</td>
<td>Incomplete closure of peritoneal and fascial layers within umbilicus by 5 yr</td>
<td>Majority asymptomatic Majority spontaneously resolve by age 5 Incarceration prior to age 5 very rare Most symptoms occur in late adolescence or adulthood</td>
<td>Protrusion from umbilicus Important to differentiate from less common abdominal wall hernias that do not spontaneously resolve (e.g. epigastric hernias) Most umbilical fascial defects &gt;1.5 cm in infancy will not close spontaneously</td>
<td>None if uncomplicated</td>
<td>Repair if not spontaneously closed by age 5 Earlier repair of large “proboscoid” hernias with extensive skin stretching may be warranted for cosmetic reasons Simple primary closure of fascial defect</td>
<td>Low risk of recurrence</td>
</tr>
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<td><strong>Intestinal Atresia</strong></td>
<td>Incidence 2-14% May be antenatally diagnosed by dilated bowel loops or “double-bubble” sign on x-ray for duodenal atresia Decreasing with increasing age</td>
<td>Duodenal – failure of bowel to recanalize after endodermal epithelium proliferation (wk 8-10) Jejunal/ileal – acquired as a result of vascular disruption → ischemic necrosis → resorption of necrotic tissue → blind distal and proximal ends Colonic – mechanism unknown, thought to be similar to small bowel atresia</td>
<td>Gastric distension and vomiting (usually bilious) Duodenal – may be associated with other anomalies (tracheoesophageal fistula, cardiac, renal, and vertebral anomalies), 24-28% have Down syndrome Jejunal/ileal – within 2-3 d of birth, may be associated with CF Colonic – within 3 d of birth</td>
<td>Complete physical Special attention to abdominal exam Perineum and anus Include evaluation of respiratory distress and signs of volume depletion Congential anomalies Jaundice</td>
<td>Contrast enema ± UGI with small bowel follow-through (SBFT) Group and screen INR and PTT if for surgery</td>
<td>NPO NGT decompression Fluid resuscitate TPN Broad spectrum antibiotics Duodenal – duodenoduodenostomy or duodenojejunostomy Jejunal/ileal – primary anastomosis; or if atresia associated with short bowel then may create end stoma or defer surgery for bowel lengthening procedures Colonic – primary anastomosis</td>
<td>Long-term survival Duodenal – 86% Jejunal/Ileal – 84% Colonic – 100%</td>
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<td>1.5,000 births M:F = 3:1 to 4:1, approaches 1:1 when whole colon involved Can have aganglinois of small bowel as well Familial Hirschsprung’s in &lt;5% of cases</td>
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<td>2-5% of term males – most of these descend spontaneously by 6 mo of age 1% of males do not spontaneously descend</td>
<td>Idiopathic: Descent is mediated by descidin which is created in response to testosterone Descent usually begins at 28 wk</td>
<td>Palpable testicle within inguinal canal or testicle which can be milked down into scrotum (called retractile testis) Occasionally no palpable testis as it is intra-abdominal Consider other congenital abnormalities</td>
<td>Bi-annual testicular exam with palpation Distinguish truly undescended testis from retractile tests (which is “high” tests due to hyperactive cremasteric muscles)</td>
<td>Depends on age of presentation U/S or MRI if no palpable testis Older child: LH, FSH, MIS, hCG stimulation test for gonadotropin production Infant: U/S, FSH, LH, karyotype, MIS, 17-hydroxyprogesterone</td>
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| **Intussusception** | Most common cause of bowel obstruction between the ages of 6-36 mo  
26/100,000 newborns  
M:F = 3:2  
Pathologic lead points: enlarged Peyer’s patches due to viral infections of the GI tract, polyps, Meckel’s diverticulum  
CF, lymphoma, IBD may increase risk | Idiopathic is most common  
Usually starts at ileocecal junction  
Telescoping of bowel into itself causing an obstruction and vascular compromise | Acute onset of abdominal pain which is classic episodic “colicky” pain  
Vomiting ± bilious  
Abdominal mass  
Curtain-jevy stool suggests mucosal necrosis and sloughing | Abdominal exam  
Palpate for masses (especially sausage shaped upper abdominal mass) and tenderness  
Signs of bowel obstruction: distended abdomen  
Look for localized peritonitis which suggests transmural ischemia | AXR for signs of bowel obstruction or perforation  
US if suspect pathology | If peritonitis, then consider operative management  
Non-operative management involves reduction via air contrast enema  
Operative reduction can be done open or laparoscopically  
Resection of involved colon if failure to reduce or bowel appears compromised | 10% recurrence rate  
If recurrent = more likely non-idiopathic  
In successfully reduced by enema in older children allow 2 wk resolution of edema then perform SBFT to rule out pathologic lead points |
| **Tracheoesophageal Fistula (TEF)** | 1:3,000-1:4,500  
Associated anomalies in 50%: VACTERL association (see Pediatrics, P42) | Varies with type of fistula  
May have history of maternal polyhydramnios  
May present after several months (if no associated esophageal atresia) of non-bilious vomiting, coughing, cyanosis with feeds; respiratory distress, recurrent pneumonia, frothy bubbles of mucus in mouth and nose that return after suctioning | X-ray: anatomic abnormalities, NGT curled in pouch | Investigate for other congenital anomalies, early repair by surgical ligation to prevent lung damage and maintain nutrition and growth | Complications: pneumonia, sepsis, reactive airways disease  
Following repair: esophageal stenosis and strictures at repair site, GERD and poor swallowing (i.e. dysphagia, regurgitation) |
| **Inguinal Hernias** | 5% of all term newborns  
2x risk and more likely bilateral if pre-term  
M:F = 4:1  
Low birth weight increases risk  
1/5 inguinal hernias will become incarcerated if patient is <1 yr old  
Incarceration is more common in females  
Associated with other conditions: androgen insensitivity, connective tissue diseases | All infant hernias are indirect: descent of intra-abdominal contents through the internal inguinal ring through a patent tunica vaginalis  
Most common presentation: painless intermittent mass in groin, may also note extension into scrotum (scrotal mass in absence of inguinal mass is a hydrocele)  
If incarcerated: tender, vomiting, firm mass, erythema then cyanosis of mass may be noted | Palpate for “bag of worms” suggests possible testicular varicocele  
Biannual testicular exam + palpation along inguinal canal to evaluate for any masses  
“Silk sign” – palpable thickening of cord Mass palpated at external inguinal ring and reducible through inguinal canal into abdomen  
Must always try reduction to confirm that hernia is not incarcerated | Physical exam is gold standard  
U/S only if physical exam uncertain (e.g. in small infants where exam can be difficult)  
Manual reduction – to relieve acute symptoms  
Herniorrhaphy – definitive treatment by reduction of herniated contents and high ligation of sac for indirect hernias  
Laparoscopic or open techniques | Risk of recurrence after surgical reduction <3% but higher if repair done in premature infants or if hernia was incarcerated/strangulated at repair |

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**Skin Lesions**

- see Dermatology, D35; Emergency Medicine, ER17; Plastic Surgery, PL5

All inguinal hernias of infancy and childhood require repair at the earliest convenience; emergent repair if incarcerated/strangulated at repair.
Common Medications

Antiemetics
- dimenhydrinate (Gravol®) 25-50 mg PO/IV/IM q4-6h pm
- prochlorperazine (Stemetil®) 5-10 mg PO/IV/IM bid-tid pm
- metoclopramide (Maxeran®) 10 mg IV/IM q2-3h pm, 10-15 mg PO qid (30 min before meals and qhs)
- ondansetron (Zofran®) 4-8 mg PO q8h pm
- granisetron (Kytril®) 1 mg PO bid (for nausea from chemotherapy/radiation)

Analgesics
- acetaminophen ± codeine (Tylenol®/3) #2 plain 1-2 tabs q4-6h PO/PR pm
- hydroxyzine i.v. i.m. tabs PO q4h pm, 0.5-2 mg IV q3-4h pm
- ibuprofen 200-400 mg PO q4-6h pm
- morphine 2.5-10 mg IM/SC q4-6h pm + 1-2 mg IV q1h pm for breakthrough
- ketorolac (Toradol®) 30-60 mg IM/IV q6h pm
- Percocet® (acetaminophen/oxycodone, 325/5 mg) 1-2 tabs PO q4-6h pm

DVT Prophylaxis
- heparin 5,000 units SC bid, if cancer patient then heparin 5,000 units SC tid
- dalteparin (Fragmin®) 4,000 units SC daily
- enoxaparin (Lovenox®) 40 mg SC daily

Antidiarrheals
- imodium (Imodium®) 4 mg PO initially, then 2 mg PO after each loose stool up to 16 mg/d
- diphenoxylate + atropine (Lomotil®) 2 tabs/10 mL PO qid

Laxatives
- sennosides (Senokot®) 1-2 tabs qhs
- docusate sodium (Colace®) 100 mg PO bid
- glycerine suppository 1 tab PR pm
- lactulose 15-30 mL PO qid pm
- milk of magnesia (MOM) 30-60 mL PO qid pm
- bisacodyl (Dulcolax®) 5 mg PO pm

Sedatives
- zopiclone (Imovane®) 5-7.5 mg PO qhs pm
- lorazepam (Ativan®) 0.5-2 mg PO/SL qhs pm

Antibiotics
- cefazolin (Ancef®) 1 mg IV/IM on call to OR or q8h – GP except Enterococcus, GN only E. coli, Klebsiella, and Proteus
- cefalexin (Keflex®) 250-500 mg PO qid – Listeria, GP except Enterococcus, GN only E. coli, Klebsiella, and Proteus
- ceftaxone (Zinacef®) 1-2 g IV/IM q2h – broad coverage including Pseudomonas
- ampicillin 1-2 g IV q6h – Listeria, GP (Enterococcus) except Streptococcus and E. coli, oral anaerobes except Bacteroides
- gentamicin 3-5 mg/kg/d IV/IM divided q8h; monitor creatinine, gentamicin levels – GN including Pseudomonas
- ciprofloxacin 400 mg IV q2h, 500 mg PO bid – GN including Pseudomonas
- metronidazole (Flagyl®) 500 mg PO/IV bid (500 mg PO tid for C. difficile) – anaerobes
- clindamycin 600-900 mg IV q8h, 150-400 mg PO qid – GP except Enterococcus, anaerobes
- pipercillin/tazobactam 4.5 mg IV q6h – GP, GN, and anaerobes
- vancomycin 1g IV q12h – GM and MRSAs
- sulfamethoxazole/trimethoprim DS (Septra®) PO bid – GM, GN including nocardiace

Over-the-Counter Medications
- Pepto-Bismol® (bismuth subsalicylate) 2 tabs or 30 mL PO q30min-1h up to 8 doses/d
- Rolaids® (calcium carbonate and magnesium hydroxide) 2-4 tabs PO q1h pm, max 12 tabs/d

References

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Ayan Dey, chapter editor
Hart Stadnick and Kevin Yau, associate editors
Alex Cressman, EBM editor
Dr. Barry J. Goldlist, staff editor

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Acronyms

ACEI  angiotensin converting enzyme inhibitor
ADL  activities of daily living
ARB  angiotensin receptor blocker
BPH  benign prostatic hypertrophy
CABG  coronary artery bypass graft
CBT  cognitive behavioural therapy
CHF  congestive heart failure
CO  cardiac output
CVA  cerebrovascular accident
DHPPCB  dihydropyridine calcium channel blocker
DM  diabetes mellitus
DNR  do not resuscitate
ESAS  Edmonton symptom assessment scale
FAP  familial adenomatous polyposis
giant cell arteritis
GCA  heart rate
IBD  inflammatory bowel disease
ICD  intracranial pressure
ICH  intracerebral hemorrhage
ICP  ICU
ICU  intensive care unit
INR  international normalized ratio
IPPS  institutional performance improvement program
IV  intravenous
MMSE  mini mental status examination
NE  norepinephrine
NG  nasogastric
NSTEMI  non-ST elevation myocardial infarction
PCI  percutaneous coronary intervention
PPI  proton pump inhibitor
PPS  palliative performance scale
PTH  parathyroid hormone
RA  rheumatoid arthritis
SLE  systemic lupus erythematosus
UTI  urinary tract infection
Seniors in Canada and the U.S.

Health Status

Table 1. Causes of Mortality and Morbidity in Canadian and American Seniors

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<th>Morbidity¹²</th>
</tr>
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<tr>
<td>1. Diseases of the heart and circulatory system (19.7/27.0%)</td>
<td>1. Hypertension</td>
</tr>
<tr>
<td>2. Malignant neoplasms (29.9/22.0%)</td>
<td>2. Arthritis</td>
</tr>
<tr>
<td>3. Cerebrovascular disease (5.5/6.0%)</td>
<td>3. Heart disease</td>
</tr>
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<td>4. Chronic lower respiratory disease (4.6/7.0%)</td>
<td>4. Diabetes</td>
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<tr>
<td>5. Accidents (4.4%)</td>
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<tr>
<td>6. Alzheimer’s (2.6/5.0%)</td>
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¹Statistics Canada, 2011  ²Minino AM, 2009

Physiology and Pathology of Aging

Definition

• major categories of impairment that appear with old age and affect the physical, mental, and social domains of the elderly, usually due to many predisposing and precipitating factors, rather than a single cause

Table 2. Changes Occurring Frequently with Aging

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<thead>
<tr>
<th>System</th>
<th>Physiological Changes</th>
<th>Pathological Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurologic</td>
<td>Decreased wakefulness, brain mass, cerebral blood flow,</td>
<td>Increased insomnia, neurodegenerative disease, stroke, decreased reflex</td>
</tr>
<tr>
<td></td>
<td>white matter changes</td>
<td>response</td>
</tr>
<tr>
<td>Special Senses</td>
<td>Decreased lacrimal gland secretion, lens transparency,</td>
<td>Increased glaucoma, cataracts, macular degeneration, presbycusis,</td>
</tr>
<tr>
<td></td>
<td>dark adaptation, decreased sense of smell and taste</td>
<td>presbyopia, tinnitus, vertigo, oral dryness</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased sBP, dBP, decreased HR, CO</td>
<td>Increased atherosclerosis, CAD, MI, CHF, hypertension, arrhythmias</td>
</tr>
<tr>
<td></td>
<td>Decreased vessel elasticity, cardiac myocyte size and</td>
<td></td>
</tr>
<tr>
<td></td>
<td>number, β-adrenergic responsiveness</td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>Increased tracheal cartilage calcification, mucus gland</td>
<td>Increased COPD, pneumonia, pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>hypertrophy</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Increased intestinal villous atrophy</td>
<td>Increased cancer, diverticulitis, constipation, fecal incontinence,</td>
</tr>
<tr>
<td></td>
<td>Decreased esophageal peristalsis, gastric acid secretion,</td>
<td>hemorrhoids, intestinal obstruction</td>
</tr>
<tr>
<td></td>
<td>liver mass, hepatic blood flow, calcium and iron absorption</td>
<td></td>
</tr>
<tr>
<td>Renal and Urologic</td>
<td>Increased proteinuria, urinary frequency</td>
<td>Increased urinary incontinence, nocturia, BPH, prostate cancer,</td>
</tr>
<tr>
<td></td>
<td>Decreased renal mass, creatinine clearance, urine</td>
<td>pyelonephritis, nephrolithiasis, UTI</td>
</tr>
<tr>
<td></td>
<td>acidification, hydroxylation of vitamin D, bladder capacity</td>
<td></td>
</tr>
<tr>
<td>Reproductive</td>
<td>Decreased androgen, estrogen, sperm count, vaginal</td>
<td>Increased breast and endometrial cancer, cystocele, rectocele, atrophic</td>
</tr>
<tr>
<td></td>
<td>secretion</td>
<td>vaginitis</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Increased NE, PTH, insulin, vasopressin</td>
<td>Increased DM, hypothyroidism, stress response</td>
</tr>
<tr>
<td></td>
<td>Decreased ovary, uterus, vagina, breast size</td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Increased calcium loss from bone</td>
<td>Increased arthritis, bursitis, osteoporosis, muscle weakness with</td>
</tr>
<tr>
<td></td>
<td>Decreased muscle mass, cartilage</td>
<td>gait abnormalities, polymyalgia rheumatic</td>
</tr>
<tr>
<td>Integumentary</td>
<td>Atrophy of sebaceous and sweat glands</td>
<td>Increased lentigo, cherry hemangiomas, pruritus, seborrheic keratosis,</td>
</tr>
<tr>
<td></td>
<td>Decreased epidermal and dermal thickness, dermal</td>
<td>herpes zoster, decubitus ulcers, skin cancer</td>
</tr>
<tr>
<td></td>
<td>vascularity, melanocytes, collagen synthesis</td>
<td></td>
</tr>
<tr>
<td>Psychiatric</td>
<td>None</td>
<td>Increased depression, dementia, delirium, suicidality, anxiety, sleep</td>
</tr>
<tr>
<td></td>
<td></td>
<td>disruption</td>
</tr>
</tbody>
</table>

Geriatric Giants

• Memory (cognitive function)
• Falls
• Incontinence
• Polypharmacy

5 Is of Geriatrics

Immobility
Intellect
Incontinence
Iatrogenesis
Impaired homeostasis

Most Common Acute Disorders in the Elderly

• Cardiovascular disease (CHF, CVA, MI)
• Fracture (hip, vertebral, wrist)
• Medication-related
• Pneumonia
• Sepsis

Most Common Chronic Disorders in the Elderly

• Arthritis
• Cataracts and other visual problems
• COPD
• Cardiovascular disease
• DM (Type 2)
• Hearing impairment
• Hypertension
• Mental disorders
• Orthopedic disorders
• Sinusitis
Differential Diagnoses of Common Presentations

Constipation

- see Gastroenterology, G24

**Definition**
- less than 3 bowel movements in one wk and/or hard stools, straining, sense of blockade, needing manual maneuvers or incomplete evacuation on more than 25% of occasions for at least 12 wk (does not need to be consecutive)

**Epidemiology**
- chronic constipation increases with age (up to 1/3 of patients >65 yr experience constipation and 1/2 of patients >80)

**Pathophysiology**
- impaired rectal sensation (increased rectal distention required to stimulate the urge to defecate)
- colorectal dysmotility

**Treatment**
- non-pharmacological
  - increase fibre intake
  - ensure adequate fluid intake
  - discourage chronic laxative use
  - engage in regular exercise
  - review medication regime, reduce dosages or substitute
- pharmacologic
  - see Common Medications, GM15

Risk Factors for Constipation in the Elderly Include:
- Immobility
- Diet: low fibre/calorie diet, dehydration
- Medications: polypharmacy
- Drugs: narcotics, calcium channel blockers, anticholinergics
- GI: obstructive lesions (bowel obstruction, cancer, diverticular disease, IBD, strictures, uterine prolapse), altered colonic motility (IBS, colonic inertia)
- Neurological: spinal cord injury, Parkinson’s disease, stroke, autonomic dysfunction
- Metabolic: diabetes, hypokalemia, hypercalcemia
- Psychiatric: depression, dementia

Delirium, Dementia, and Depression

- see Psychiatry, PS20, PS21, PS11 and Neurology, N21

**Definition**
- pathologic decrease in memory, language, or executive function

**Differential Diagnosis**
- delirium, dementia, or pseudodementia of depression
Table 3. Differentiating the Three Ds of Cognitive Impairment

<table>
<thead>
<tr>
<th>Dementia</th>
<th>Delirium</th>
<th>Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual or step-wise decline</td>
<td>Acute (hours-d)</td>
</tr>
<tr>
<td>Duration</td>
<td>Mo-yr</td>
<td>D-wk</td>
</tr>
<tr>
<td>Natural History</td>
<td>Progressive, usually irreversible</td>
<td>Fluctuating, reversible</td>
</tr>
<tr>
<td></td>
<td></td>
<td>High morbidity/mortality in very old</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Normal</td>
<td>Fluctuating</td>
</tr>
<tr>
<td>Attention</td>
<td>Intact initially</td>
<td>Decreased, wandering</td>
</tr>
<tr>
<td>Orientation</td>
<td>Intact initially</td>
<td>Impaired, fluctuates</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Disinhibition, loss of ADL/ IADLs, personality change</td>
<td>Severe agitation/retardation</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
</tr>
<tr>
<td>Sleep-Wake Cycle</td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep-wake cycle</td>
</tr>
<tr>
<td>Mood and Affect</td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
</tr>
<tr>
<td>Cognition</td>
<td>Decreased executive function, paucity of thought</td>
<td>Fluctuation preceded by mood changes</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
</tr>
<tr>
<td>Language</td>
<td>Agnosia, aphasia, decreased comprehension, repetition</td>
<td>Dysnomia, dysgraphia, speech rambling, subject changes, incoherence</td>
</tr>
<tr>
<td>Delusions</td>
<td>Compensatory</td>
<td>Nightmarish, poorly formed</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable, vacuous, bland</td>
<td>Visual common, frightening/bizarre</td>
</tr>
</tbody>
</table>

Delirium Prevention in Elderly
- Ensure optimal vision and hearing to support orientation (e.g., appropriate eye wear and hearing aids)
- Provide adequate nutrition and hydration (up in chair to eat and drink whenever feasible)
- Encourage regular mobilization to build and maintain strength, balance, and endurance
- Avoid unnecessary medications and monitor for drug interactions
- Avoid bladder catheterization if possible
- Ensure adequate sleep

Elder Abuse

Definition
- Includes physical abuse, sexual abuse, emotional/psychological abuse, financial abuse, abandonment, and neglect
- Elder abuse is a criminal offence under the Criminal Code of Canada
- In the U.S., most states have criminal penalties for elder abuse

Epidemiology
- In Canada in 2004, 3,370 incidents of violence against individuals aged ≥65 were reported
  - 29% of these incidents were committed by a family member
- In Canada in 2004, there were 50 homicides committed against seniors
- In the U.S., estimates of the frequency of elder abuse range from 3-8%
- Physician reporting is mandatory only in Newfoundand, Nova Scotia, and Prince Edward Island; in Ontario, only abuse occurring in nursing homes is mandatory to report
- Insufficient evidence to exclude/screening in the Periodic Health Exam

Risk Factors

Table 4. Risk Factors for Elder Abuse

<table>
<thead>
<tr>
<th>Situational Factors</th>
<th>Victim Characteristics</th>
<th>Perpetrator Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolation</td>
<td>Physical or emotional dependence on caregiver</td>
<td>Related to victim</td>
</tr>
<tr>
<td>Unstable or unsafe living arrangements</td>
<td>Lack of family, community or living facility resources for additional care</td>
<td>Living with victim</td>
</tr>
<tr>
<td>Lack of family, community or living facility resources for additional care</td>
<td>History of family violence</td>
<td>Long duration of care for victim (mean 9.5 yr)</td>
</tr>
<tr>
<td>Physical or emotional dependence on caregiver</td>
<td>Dementia or recent deterioration in health</td>
<td>Financial, marital, occupational or other stressors</td>
</tr>
<tr>
<td>Lack of close family ties</td>
<td>History of family violence</td>
<td>Long duration of care for victim (mean 9.5 yr)</td>
</tr>
</tbody>
</table>
Caregiver Abuse Screen (CASE)

- **instructions**
  - to be answered by caregivers, if answer “yes” to a question, further explore issue
  - the more “yes” responses, the more likely the presence of abuse
  - screening tool
  - please answer the following questions as a helper/caregiver:
    1. Do you sometimes have trouble making _____ control his/her temper or aggression?
    2. Do you sometimes feel that you are forced to do things you feel badly about?
    3. Do you find it difficult to manage _____’s behavior?
    4. Do you sometimes feel that you are forced to be tough with _____?
    5. Do you sometimes feel that you can’t do what is really necessary or what should be done for _____?
    6. Do you often feel you have to reject/ignore _____?
    7. Do you often feel so tired and exhausted that you cannot meet _____’s needs?
    8. Do you often feel you have to yell at _____?

From: NICE. Caregiver Abuse Screen. 2010. Reproduced with permission from NICE.

Management

- assess safety and determine capacity to make decisions about living arrangements
- establish need for hospitalization or alternate accommodation (e.g. immediate risk of physical harm by self or caregiver)
- involve multidisciplinary team (e.g. nurse, social worker, family members, and physicians including geriatrician, psychiatrist or family physician)
- educate and assist caregiver, contact local resources (e.g. legal aid, crisis support, PSW, caregiver support groups)
- interpret critical and lab findings that are key in exclusion, differentiation and diagnosis

Falls

Definition

- an event which results in a person coming to rest inadvertently on the ground or floor or other lower level

Epidemiology

- 30-40% of people >65 yr old and ~50% of people >80 yr old fall each year
  - equally common between men and women, but more likely to result in injury in women and death in men
  - 5% of falls lead to hospitalization
  - falls are the leading cause of death from injury in persons older than 65 yr
  - 25% associated with serious injuries (e.g. hip fracture, head injury, bruises, laceration)
  - between 25-75% do not recover to previous level of ADL function
  - mortality increases with age (171/100,000 in men >85 yr old) and type of injury (25% with hip fracture die within 6 mo)

Etiology

- multifactorial
- extrinsic
  - environmental (e.g. home layout, lighting, stairs, overcrowding)
  - accidental, abuse
  - side effects of medications and substance abuse (e.g. alcohol)
  - acute illness, exacerbation of chronic illness
- intrinsic
  - orthostatic/syncopal
  - age-related changes and diseases associated with aging: musculoskeletal (arthritis, muscle weakness), sensory (visual, proprioceptive, vestibular), cognitive (depression, dementia, delirium, anxiety), cardiovascular (CAD, arrhythmia, MI, low BP), neurologic (stroke, decreased LOC, gait disturbances/ataxia), metabolic (glucose, electrolytes)

Investigations

- directed by history and physical
- comprehensive geriatric assessment to identify all potential causes
- CBC, electrolytes, BUN, creatinine, glucose, Ca²⁺, TSH, B₁₂, urinalysis, cardiac enzymes, ECG, CT head

Prevention

- multidisciplinary, multifactorial, health, and environmental risk factor screening and intervention programs in the community
- muscle strengthening, balance retraining, and group exercise programs (e.g. Tai Chi)
- home hazard assessment and modification (e.g. remove rugs, add shower bars, etc.)
- prescription of vitamin D 1000 IU daily
- tapering or gradually discontinuation of psychotropic medication
- postural hypotension, heart rate, and rhythm abnormalities management
- eyesight and footwear optimization

Adapted from: Am Fam Phys 2001;61:2159-2172

Did a fall occur in the past year?

Single fall

Administer standardized gait and balance test

Recurrent falls

Administer multifactorial falls assessment

**Step 1**
Take focused history screening for:
- History of falls
- Medication review
- History of relevant risk factors

**Step 2**
Conduct physical examination, focusing on:
- Gait balance, and mobility
- Neurological function
- Muscle strength of the lower extremities
- Cardiovascular status
- Visual acuity
- Feet and footwear

**Step 3**
Conduct environmental assessment, including home safety inspection

**Step 4**
Perform functional assessment including:
- Activities of daily living
- Use of adaptive equipment and mobility aids
- Perceived fear related to falling

**Step 5**
Perform interventions based on findings of Step 1-4 assessments (rated on a scale of A-D; A=strong support, D=weak support):
- Adapt or modify home environment (A)
- Exercise, particularly balance and strength training (C)
- Withdraw or minimize use of hypnotics and antipsychotics (B)
- Withdraw or minimize use of other contributory medications (C)
- Manage postural hypotension (C)
- Manage foot problems or footwear (C)

Figure 2. Approach to falls in the elderly
Adapted from: Davuluri S, Dharmarajan TS. Clinical Geriatrics 2013;21(10)

### Frailty (Progressive Functional Decline/Failure to Thrive)

**Definition**
- Declining independence and functional capacity with loss of energy, vigor, and/or weight in older adults
- Not an inevitable consequence of aging

**Etiology**
- Malnutrition, functional impairment, cognitive impairment, and depression

**Table 5. Common Medical Conditions Associated with Failure to Thrive**

<table>
<thead>
<tr>
<th>Medical Condition</th>
<th>Cause of Failure to Thrive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Metastases, malnutrition, cachexia</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>Respiratory failure</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Chronic steroid use</td>
<td>Steroid myopathy, diabetes, osteoporosis, vision loss</td>
</tr>
<tr>
<td>Cirrhosis, hepatitis</td>
<td>Hepatic failure</td>
</tr>
<tr>
<td>Depression, other psychiatric disorder</td>
<td>Major depression, psychosis, poor functional status, cognitive loss</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Malabsorption, poor glucose homeostasis, end-organ damage</td>
</tr>
<tr>
<td>Gastrointestinal surgery</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Hip, long bone fracture</td>
<td>Functional impairment</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Malabsorption, malnutrition</td>
</tr>
<tr>
<td>Myocardial infarction, congestive heart failure</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>Recurrent UTI, pneumonia</td>
<td>Chronic infection, functional impairment</td>
</tr>
<tr>
<td>Rheumatologic disease (GCA, RA, SLE)</td>
<td>Chronic inflammation</td>
</tr>
<tr>
<td>Stroke</td>
<td>Dysphagia, depression, cognitive loss, functional impairment</td>
</tr>
<tr>
<td>Tuberculosis, other systemic infection</td>
<td>Chronic infection</td>
</tr>
</tbody>
</table>

Adapted from: Clin Geriatr Med 1997;12:769-778
Incontinence

Fecal Incontinence

Definition

- involuntary passage or the inability to control the discharge of fecal matter through the rectum
- severity can range from unintentional flatus to the complete evacuation of bowel contents
- there are three subtypes
  1. passive incontinence: involuntary discharge of stool or gas without awareness
  2. urge incontinence: discharge of fecal matter in spite of active attempts to retain bowel contents
  3. fecal seepage: leakage of stool following otherwise normal evacuation

Epidemiology

- second leading cause of nursing home placement
- US estimates show that 10-25% of hospitalized geriatric patients suffer from fecal incontinence

Etiology

- commonly multifactorial
  - structural abnormalities
  - trauma (e.g. prior vaginal delivery, surgery)
  - prolapse
  - tumour/trauma (e.g. brain, spinal cord, cauda equina)
  - overflow (e.g. encopresis, impaction)
  - functional abnormalities
  - neurologic conditions – neuropathy, multiple sclerosis, stroke, dementia
  - others
    - constipation with overflow may be a factor
    - psychosis (willful soiling)
    - age >80 yr: decreased external sphincter strength and weak anal squeeze, increased rectal compliance, decreased resting tone and internal sphincter, impaired anal sensation
    - medications (e.g. laxatives, anticholinergics, antidepressants, caffeine, muscle relaxants)

Factors in Prevention/Management

- Lifestyle changes
- Medications
- Physical therapy
- Education
- Support

Indicators

- Depression
- Malnutrition
- Cognitive impairment
- Functional impairment (decreased mobility)

Limited laboratory tests and radiologic survey

MMSE, ADL, and IADL scales

“Up and Go Test”

Geriatric Depression Scale

Nutritional assessment

Medication review

Chronic disease evaluation

Environmental assessment

If response is positive, continue to treat*

If no or minimal response, conduct conference with patient, patient’s family, and caregivers

Repeat evaluations, if appropriate

Consider discussion of end-of-life and hospice options

* A positive response is defined as achievement of set pretreatment goals, as determined by the patient, the patient’s family, and participating caregivers.

Figure 3. Failure to thrive in elderly patients
Adapted from: American Family Physician 2004;70: 343-350
**Investigations (if cause not apparent from history and physical)**
- differentiate true incontinence from frequency and urgency (i.e. IBS, IBD)
- stool studies
- endorectal ultrasound
- colonoscopy, sigmoidoscopy, anoscopy
- anorectal manometry/functional testing

**Management**
- diet/bulking agent if stool is liquid or loose
- disimpaction, prevent impaction
- anti-diarrheal agents (e.g. loperamide)
- regular defecation program in patients with dementia
- counsel about biofeedback therapy (retraining of pelvic floor muscles)

**URINARY INCONTINENCE**
- see Urology, U5

**Definition**
- complaint of any involuntary loss of urine
- can be further defined according to patients symptoms as urgency urinary incontinence, stress urinary continence, mixed urinary incontinence, nocturnal enuresis, post-micturition dribble, and continuous urinary leakage

**Epidemiology**
- 15-30% prevalence dwelling in community and at least 50% of institutionalized seniors
- morbidity: cellulitis, pressure ulcers, urinary tract infections, falls with fractures, sleep deprivation, social withdrawal, depression, sexual dysfunction
- not associated with increased mortality

**Pathophysiology**
- not a normal part of aging, urinary incontinence is a loss of control due to a combination of:
  - genitourinary pathology: increased post-void residual volume, increased involuntary bladder contractions (urge incontinence)
  - age-related changes: decreased bladder capacity
  - comorbid conditions and medications
  - functional impairment
- in elderly women: decline in bladder outlet and urethral resistance pressure promoting stress incontinence
- in elderly men: prostatic enlargement can cause overflow and urge incontinence

**Gait Disorders**
- see Neurology, N36

**Hazards of Hospitalization**

<table>
<thead>
<tr>
<th>Sequele</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malnutrition</td>
<td>No dietary restrictions (except diabetes), assistance, dentures if necessary, sitting in a chair to eat</td>
</tr>
<tr>
<td>Urinary incontinence</td>
<td>Medication review, remove environmental barriers, discontinue use of catheter</td>
</tr>
<tr>
<td>Depression</td>
<td>Routine screening</td>
</tr>
<tr>
<td>Adverse drug event</td>
<td>Medication review</td>
</tr>
<tr>
<td>Confusion/delirium</td>
<td>Orientation, visual and hearing aids, volume repletion, noise reduction, early mobilization, medication review, remove restraints</td>
</tr>
<tr>
<td>Pressure ulcers</td>
<td>Low-resistance mattress, daily inspection, repositioning every 2 h</td>
</tr>
<tr>
<td>Infection</td>
<td>Early mobilization, remove unnecessary IV lines, catheters, NG tubes</td>
</tr>
<tr>
<td>Falls</td>
<td>Appropriate footwear, assistive devices, early mobilization, remove restraints, medication review</td>
</tr>
<tr>
<td>Hypotension/dehydration</td>
<td>Early recognition and repletion</td>
</tr>
<tr>
<td>Diminished aerobic capacity/loss of muscle strength/contractures</td>
<td>Early mobilization</td>
</tr>
<tr>
<td>Decreased respiratory function</td>
<td>Incentive spirometry, physiotherapy</td>
</tr>
</tbody>
</table>
Hypertension

Definition
- see Family Medicine, FM35

Definition
- blood pressure at which an otherwise healthy person would have increased risk of cardiovascular disease
- definition of high blood pressure has changed over time and differs between guidelines proposed by expert bodies
- target: <140/90 mm Hg for adults younger than 60. <130/80 mm Hg for individuals with DM. <150/90 for adults aged 60 or older

Epidemiology
- 60-80% of elderly (>65 yr old) have hypertension
  - 60% of these have isolated systolic HTN
  - the benefit of treating hypertension in the elderly is 2-4 times greater than that achieved in the treatment of younger patients with primary hypertension
  - systolic and pulse pressure are major predictors of outcome in the elderly patient
  - in older adults, base treatment on sBP

Management
- non-pharmacologic treatments are first-line, then thiazide monotherapy is recommended
  - add ACEI/ARB if also atherosclerosis, DM, CHF or chronic kidney disease
  - add β-blockers if also angina or CHF

Complications
- cardiovascular: orthostatic hypotension, venous thrombosis, embolism
- respiratory: decreased ventilation, atelectasis, pneumonia
- gastrointestinal: anorexia, constipation, incontinence, dehydration, malnutrition
- genitourinary: infection, urinary retention, bladder calculi, incontinence
- musculoskeletal: atrophy, contractures, bone loss
- skin: pressure ulcers
- psychological: sensory deprivation, delirium, depression

Immunizations
- the following immunizations are recommended for people 65 yr of age and older
  - tetanus: every 10 yr
  - pneumococcus: every 5 yr
  - influenza: every autumn
  - herpes zoster: Zostavax®

Malnutrition

Definition
- involuntary weight loss of ≥5% baseline body weight or ≥5 kg
- hypoalbuminemia, hypcholesterolemia

Etiology
- nutritional
  - decreased assimilation: impaired transit, maldigestion, malabsorption
  - decreased intake: financial, psychiatric (depression), cognitive deficits, anorexia associated with chronic disease, functional deficits (e.g. difficulty shopping, preparing meals or feeding oneself due to functional impairment)
- stress: acute or chronic illness/infection, chronic inflammation, abdominal pain
- mechanical: dental problems, dysphagia
- age-related changes: appetite dysregulation, decreased thirst
- mixed: increased energy demands (e.g. hyperthyroidism), abnormal metabolism, protein-losing enteropathy

Etiology of Malnutrition in the Elderly
- MEALS ON WHEELS
- Medications
- Emotional problems
- Anorexia
- Late-life paranoia
- Swallowing disorders
- Oral problems
- Nosocomial infections
- Wandering/dementia related activity
- Hyperthyroid/Hypercalcemia/
- Hypoaldenism
- Enteric disease
- Eating problems
- Low-salt/Low-fat diet
- Stones
Clinical Features

- history
  - recent or chronic illness
  - depression, GI symptoms
  - functional disability: impaired ADLs and IADLs
  - social factors: economic barriers, dental problems and living situation (e.g. living alone)
  - constitutional symptoms (e.g. recent weight loss)
- physical exam
  - BMI <23.5 in males, <22 in females should raise concern
  - temporal wasting, muscle wasting, presence of triceps skin fold
  - assess cognition

Investigations

- CBC, electrolytes, Ca^{2+}, Mg^{2+}, PO_{4}^{3-}, creatinine, LFTs (albumin, INR, bilirubin), B_{12}, folate, TSH, transferrin, lipid profile, urinalysis, ESR, CXR

Osteoporosis

- see Endocrinology, E42

Presbycusis

- see Otolaryngology, OT20

Pressure Ulcers

- see Plastic Surgery, PL16

Risk Factors

- extrinsic factors: friction, pressure, shear force
- intrinsic factors: immobility, malnutrition, moisture, sensory loss

Table 7. Classification of Pressure Ulcers

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Changes include skin temperature, tissue consistency or sensation</td>
</tr>
<tr>
<td></td>
<td>An area of persistent erythema in lightly pigmented, intact skin; in darker skin, it may appear red, blue or purple</td>
</tr>
<tr>
<td>Stage II</td>
<td>Partial thickness skin loss involving the epidermis, dermis or both</td>
</tr>
<tr>
<td></td>
<td>The ulcer is superficial and presents as an abrasion, blister or shallow crater</td>
</tr>
<tr>
<td>Stage III</td>
<td>Full thickness skin loss involving damage or necrosis of subcutaneous tissue which may extend down to, but not through, underlying fascia</td>
</tr>
<tr>
<td></td>
<td>Presents as a deep crater with or without undermining of adjacent tissue</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Full thickness skin loss with extensive destruction, tissue necrosis or damage to muscle, bone or supporting structures</td>
</tr>
<tr>
<td></td>
<td>May have associated undermining and/or sinus tracts</td>
</tr>
</tbody>
</table>

Prevention

- pressure reduction
  - frequent repositioning
  - pressure-reducing devices (static, dynamic)
- maintaining nutrition, encouraging mobility and managing incontinence

Treatment

- optimize nutritional status
- minimize pressure on wound
- analgesia
- wound debridement (mechanical, enzymatic, autolytic) and dressing application
- maintain moist wound environment to enable re-epithelialization
- treatment of wound infections (topical gentamicin, silver sulfadiazine, mupirocin)
- swab wounds not demonstrating clinical improvement for C&S; biopsy chronic wounds to rule out malignancy
- stage IV ulcers typically warrant surgical debridement
- consider other treatment options
  - negative pressure wound therapy/vacuum-assisted closure (VAC)
  - biological agents: application of fibroblast growth factor, platelet-derived growth factor to wound
  - non-contact normothermic wound therapy
  - electrotherapy
Driving Competency

Reporting Requirements

- physician-reporting to the Ministry of Transportation is mandatory in all provinces and territories except in Quebec, Nova Scotia, and Alberta, where it is discretionary
- not an issue unique to geriatrics – any patient may suffer from a medical condition that impairs their ability to drive should be reported
- in the U.S., varies by state

Conditions that may Impair Driving

<table>
<thead>
<tr>
<th>Condition</th>
<th>Impairment/Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
<td>Patients with history of impaired driving and those with high probability of future impaired driving should not drive until further assessed. Alcohol dependence or abuse: if suspected, should be advised not to drive. Alcohol withdrawal seizure: must complete a rehabilitation program and remain abstinent and seizure-free for 6 mo before driving.</td>
</tr>
<tr>
<td>Blood Pressure Abnormalities</td>
<td>Hypertension: sustained BP &gt;170/110 should be evaluated carefully. Hypotension: if syncopal, discontinue until attacks are treated and preventable.</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>Suspected asymptomatic CAD or stable angina: no restrictions. STEMI, NSTEMI with significant LV damage, coronary artery bypass surgery: no driving for one mo following hospital discharge. NSTEMI with minor LV damage, unstable angina: no driving for 48 h if percutaneous coronary intervention (PCI) performed or 7 d if no PCI performed.</td>
</tr>
<tr>
<td>Cerebrovascular Conditions</td>
<td>TIA: should not be allowed to drive until a medical assessment is completed. Stroke: should not drive for at least one mo; may resume driving if functionally able; no clinically significant motor, cognitive, perceptual or vision deficits; no obvious risk of sudden recurrence; underlying cause appropriately treated; no post-stroke seizure.</td>
</tr>
<tr>
<td>COPD</td>
<td>Mild/moderate impairment: no restrictions. Moderate or severe impairment requiring supplemental oxygen: road test with supplemental oxygen.</td>
</tr>
<tr>
<td>Cognitive Impairment/Dementia</td>
<td>Moderate to severe dementia is a contraindication to driving; defined as the &quot;inability to independently perform 2 or more IADLs or any basic ADL.&quot; Patients with mild dementia should be assessed; if indicated, refer to specialized driving testing centre; if deemed fit to drive, re-evaluate patient every 6-12 mo. Poor performance on MMSE, clock drawing or Trails B suggests a need to investigate driving ability further. MMSE score alone (whether normal or low) is insufficient to determine fitness to drive.</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Diet controlled or oral hypoglycemic agents: no restrictions in absence of diabetes complications that may impair ability to drive (e.g. retinopathy, nephropathy, neuropathy, cardiovascular or cerebrovascular disease). Insulin use: may drive if no complications (as above) and no severe hypoglycemic episode in the last 6 mo.</td>
</tr>
<tr>
<td>Drugs</td>
<td>Be aware of: analgesics, anticholinergics, anticonvulsants, antidepressants, antipsychotics, opiates, sedatives, stimulants. Degree of impairment varies: patients should be warned of the medication/withdrawal effect on driving.</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>Effect of impaired hearing on ability to drive safely is controversial. Acute labyrinthitis, positional vertigo with horizontal head movement, recurrent vertigo: advise not to drive until condition resolves.</td>
</tr>
<tr>
<td>Musculoskeletal Disorders</td>
<td>Physician’s role is to report etiology, prognosis and extent of disability (pain, range of motion, coordination, muscle strength).</td>
</tr>
<tr>
<td>Post-Operative</td>
<td>Outpatient, conscious sedation: no driving for 24 h. Outpatient, general anesthesia: no driving for &gt;24 h.</td>
</tr>
<tr>
<td>Seizures</td>
<td>First, single, unprovoked: no driving for 3 mo until complete neurologic assessment, EEG, CT head. Epilepsy: can drive if seizure-free on medication and physician has insight into patient compliance.</td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>If patient is believed to be at risk due to a symptomatic sleep disorder but refuses investigation with a sleep study or refuses appropriate treatment, the patient should not drive.</td>
</tr>
<tr>
<td>Visual Impairment</td>
<td>Visual acuity: contraindicated to drive if &lt;20/50 with both eyes examined simultaneously. Visual field: contraindicated to drive if &lt;120° along horizontal meridian and 15° continuous above and below fixation with both eyes examined simultaneously.</td>
</tr>
</tbody>
</table>

N.B. guidelines included refer specifically to private driving; please see CMA guidelines for commercial driving.

Key Factors to Consider in Older Drivers

- SAFEDRIVE
- Safety record
- Attention (e.g. concentration lapses, episodes of disorientation)
- Family observations
- Alcohol abuse
- Drugs
- Reaction time
- Intellectual impairment
- Vision/Visuospatial function
- Executive functions (e.g. planning, decision-making, self-monitoring behaviours)

Systematic Review of the Efficacy of Compensatory Strategies in Persons with Dementia

<table>
<thead>
<tr>
<th>Journal</th>
<th>Title</th>
</tr>
</thead>
</table>

[55:878-884]: Study Selection: Systematic review of the case-control studies of drivers with a diagnosis of dementia. Purpose: To determine whether persons with dementia are at greater driving risk and, if so, to estimate the magnitude of this risk and determine whether there are efficacious methods to compensate for or accommodate it. Study Selection: Systematic review of the case-control studies of drivers with a diagnosis of dementia. Results: Drivers with dementia universally exhibited poorer performance on road tests and simulator evaluations. The one study that used an objective measure of motor vehicle crashes found that the crash risk in persons with dementia was 2.5 times greater than matched controls. No studies were found that examined the efficacy of methods to compensate for or accommodate the decreased driving performance. Conclusions: Drivers with dementia are poorer drivers than cognitively normal drivers, but studies have not consistently demonstrated higher crash rates. Clinicians and policy makers must take these findings into account when addressing issues pertinent to drivers with a diagnosis of dementia. |
Health Care Institutions

Table 9. Classification of Health Care Services and Institutions

<table>
<thead>
<tr>
<th>Institution/Service</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Community Support Services</strong></td>
<td>Health care services offered at home for those who can live independently at home or under the care of family members including professional health care services, personal care and support (ADL assistance), homemaking (IADL assistance), community support services (e.g. transportation, meal delivery, day programs, caregiver relief, security checks, etc.)</td>
</tr>
<tr>
<td><strong>Residential</strong></td>
<td>Divided into short (&lt;60-90 d/yr) and long (indefinite) stay</td>
</tr>
<tr>
<td>a) Seniors Affordable Housing</td>
<td>Seniors who live independently and manage their own care but prefer to live near other seniors; usually has accessibility features and rent is adjusted based on income</td>
</tr>
<tr>
<td>b) Retirement/Nursing Home</td>
<td>Residents are fairly independent and require minimal support with ADLs and IADLs; often privately owned</td>
</tr>
<tr>
<td>c) Supportive Housing</td>
<td>Residents require minimal to moderate assistance with daily activities while living independently; often rental units in an apartment and may offer some physiotherapy and rehabilitation services</td>
</tr>
<tr>
<td>d) Long-term Care/Skilled Nursing Facility</td>
<td>Around the clock nursing care and on-call physician coverage; often offers occupational therapy, physiotherapy, respiratory therapy, and rehabilitation services; may be used short-term for caregiver respite or for supportive patient care to regain strength and confidence after leaving the hospital</td>
</tr>
<tr>
<td>e) Hospice</td>
<td>Free-standing facility or designated floor in a hospital or nursing home for care of terminally ill patients and their families; focus is on quality of life and often requires prognosis ≤3 mo</td>
</tr>
</tbody>
</table>

- names of community health care institutions, types of facilities, and services offered vary between geographical locations
- factors to consider when seeking services/institutions include level of care required, support networks, duration of stay, and cost

Palliative and End-of-Life Care

Principles and Quality of Life

- support, educate, and treat both patient and family
- address physical, psychological, social and spiritual needs
- focus on symptom management and comfort measures
- offer therapeutic environment and bereavement support
- ensure maintenance of human dignity

End-of-Life Care Discussions

When to Initiate End-of-Life Care Discussions

- recent hospitalization for serious illness
- severe progressive medical condition(s)
- death expected within 6-12 mo
- patient inquires about end-of-life care

Suggested Topics for Discussion

- goals of care (disease vs. symptom management)
- advance directives, power of attorney, public guardian and trustee
- treatment options and likelihood of success
- common medical interventions
  - mechanical ventilation
  - antibiotic therapy
  - feeding tubes
- resuscitation options and likelihood of success (Full Code vs. DNR status including preferences for CPR, intubation, ICU admission, artificial hydration)

Power of Attorney

- see Ethical, Legal, and Organizational Medicine, ELOAM10

Guidance on the Management of Pain in Older People

Age and Aging 2013; 42:1-57
The three most common sites of pain in older adults are the back, leg/knee and hip. Acetaminophen should be considered first-line treatment for the management of both acute and persistent pain, particularly that which is of musculoskeletal origin. NSAIDs should be prescribed with caution and co-prescribed with a PPI.
Instructional Advance Directives

- see Ethical, Legal, and Organizational Medicine, ELOAM10

Symptom Management

Assessment Tools

- Edmonton Symptom Assessment System (ESAS): a tool that asks patients to rate the intensity of symptoms from 0 to 10 and allows for tracking of the efficacy of interventions. Assesses: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, shortness of breath, and "other problem"

- Palliative Performance Scale (PPS): a tool that uses functional status to predict survival in terminally ill patients. Assesses 5 components: ambulation, activity and evidence of disease, self-care, intake and conscious level

Source: J Palliat Care 1991;7:6-9 and Victoria Hospice Society 2006;120-121

Table 10. Management of Common End-of-Life Symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Non-Pharmacologic Management</th>
<th>Pharmacologic Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>Rule out obstruction, impaction, anorectal disease; hydration and high fibre intake; increase mobility</td>
<td>Stop unnecessary opioids and medications with anticholinergic side effects; provide stool softener (e.g. docusate sodium), increase peristalsis (e.g. senna), alter water and electrolyte secretion (e.g. magnesium hydroxide, lactulose, peg3350)</td>
</tr>
<tr>
<td>Death Rattle/Increased Pulmonary Secretions</td>
<td>Oral suctioning Discontinue unnecessary IV solutions</td>
<td>Scopolamine SC or transdermal</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>Oral hygiene q2h, ice cubes, sugarless gum</td>
<td>Artificial saliva substitutes, bethanochol, pilocarpine 1% solution as mouth rinse</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Frequent small feeds, ideally seated, keep head of bed elevated for 30 min after eating, suction as necessary</td>
<td>Oxygen, bronchodilators, opioids (e.g. morphine, hydromorphone)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>Elevate head of bed, eliminate allergens, open window/use fan</td>
<td>Oxycodone, hydroxyzine, metoclopramide, baclofen, marijuana</td>
</tr>
<tr>
<td>Hiccups</td>
<td>Dry sugar, breathing in paper bag</td>
<td>Chlorpromazine, haloperidol, metoclopramide, backofer, marijuana</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Frequent and small meals, avoid offensive strong odours, treat constipation if present</td>
<td>Raised ICP: dexamethasone Anticipatory nausea, anxiety: loraepam</td>
</tr>
<tr>
<td>Pain</td>
<td>Hot and cold compresses, music therapy, relaxation techniques, individualized program of physical activity designed to improve flexibility, strength and endurance, and cognitive behavioural therapy (CBT)</td>
<td>Noninvasive pain: non-opioids (NSAIDs, acetaminophen), weak opioids (codeine, hydrocodone, oxycodone), strong opioids (morphine, hydromorphone, oxycodone, fentanyl)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Bathing with tepid water, avoid soap, bath oils; sodium bicarbonate for jaundice</td>
<td>Neoplastic pain: anticonvulsants (gabapentin, pregabalin), antidepressants (TCAs, SSRIs), steroids (dexamethasone)</td>
</tr>
<tr>
<td>Weakness</td>
<td>Modify environment and activities to decrease energy expenditure</td>
<td>Bone pain: non-opioids, weak opioids, bisphosphonates, radiation therapy</td>
</tr>
</tbody>
</table>


WHO’s Pain Relief Ladder

Freedom from Cancer Pain
- Opioid for moderate to severe pain ± Non-opioid ± Adjunct
- Pain persisting or increasing ± Adjunct
- Opioid for mild to moderate pain ± Non-opioid ± Adjunct
- Pain persisting or increasing ± Adjunct

Death Rattle
Noise caused by the oscillatory movement of mucous secretions in the upper airway with inspiration and expiration

Nociceptive Pain
Somatic: localized to bone/skin/joint/muscle; gnawing, dull pain
Visceral: not well localized; crampy pain, pressure
Neuropathic Pain
 Burning, shooting, radiating pain; localized to dermatomal regions

Opioid Equivalent Doses (to 10 mg of IV morphine)

<table>
<thead>
<tr>
<th>Opioid</th>
<th>SC/IV dose</th>
<th>PO dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>10 mg</td>
<td>20-30 mg</td>
</tr>
<tr>
<td>Codeine</td>
<td>Not</td>
<td>180-240 mg</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Not</td>
<td>10-15 mg</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>2 mg</td>
<td>4-6 mg</td>
</tr>
<tr>
<td>Fentanyl transdermal 25 µg/h = morphine 90 µg PO/24 h, however fentanyl takes 12-16 h to reach steady state</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serum creatinine does not reflect creatine clearance in the elderly

Instead, use: 
CrCI = (weight in kg) (140 – age)/(1.23) (mL/min) (serum creatinine in µmol/L)  
Multiply by 0.85 for females
**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age Effect</th>
<th>Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong> (less significant)</td>
<td>Increased gastric pH</td>
<td>Drug-drug and drug-food interactions are more likely to affect absorption</td>
</tr>
<tr>
<td>Decreased splanchnic blood flow, GI absorptive surface and dermal vascularity; delayed gastric emptying</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>Increased total body fat and α1-glycoprotein</td>
<td>Lipophilic drugs have a larger volume of distribution</td>
</tr>
<tr>
<td>Decreased lean body mass, total body water and albumin</td>
<td>Decreased binding of acidic drugs, increased binding of basic drugs</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong> (less significant)</td>
<td>Decreased hepatic mass and hepatic blood flow; impaired phase I reactions (oxidative system)</td>
<td>Lower doses may be therapeutic</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Decreased renal blood flow, GFR, tubular secretion and renal mass</td>
<td>For every x% reduction in clearance, decrease the dose by x% and increase the interval by x%</td>
</tr>
</tbody>
</table>

**Pharmacodynamics**

**Drug Sensitivity**
- changes in pharmacokinetics as well as intrinsic sensitivity lead to altered drug responses
- increased sensitivity to warfarin, sedatives, antipsychotics, digoxin and narcotics
- decreased sensitivity to β-blockers in majority of elderly patients, though some may have increased sensitivity

**Decreased Homeostasis**
- poorer compensatory mechanisms leading to more adverse reactions (e.g. bleeding with NSAIDs/anticoagulants, altered mental status with anticholinergic/sympathomimetic/anti-Parkinsonian drugs)

**Polypharmacy**

**Definition**
- prescription, administration or use of five or more medications at the same time

**Epidemiology**
- in Canada, > 60% of elderly individuals reported using ≥5 medications
- hospitalized elderly are given an average of 10 medications during admission

**Risk Factors for Non-Compliance**
- risk of non-compliance correlates with medication factors, not age
  - number of medications – compliance with 1 medication is 80%, but drops to 25% with ≥6 medications
  - increased dosing frequency, complicated container design, financial constraints, and cognitive impairment

**Adverse Drug Reactions (ADRs)**
- any noxious or unintended response to a drug that occurs at doses used for prophylaxis or therapy
- risk factors in the elderly
  - intrinsic: comorbidities, age-related changes in pharmacokinetics and pharmacodynamics
  - extrinsic: number of medications, multiple prescribers, unreliable drug history
  - 90% of ADRs are from: ASA, analgesics, anticoagulants, antimicrobials, antineoplastics, digoxin, diuretics, hypoglycemics, steroids

**Preventing Polypharmacy**
- consider drug: safer side effect profiles, convenient dosing schedules, convenient route, efficacy
- consider patient: other medications, clinical indications, medical comorbidities
- consider patient-drug interaction risk factors for ADRs
- review drug list regularly to eliminate medications with no clinical indication or with evidence of toxicity
- avoid treating an ADR with another medication

**Approach to Medication Review in the Elderly**
- NO TEARS
  - Need and indication
  - Open-ended questions (to get patient’s perspective on medications)
  - Tests and monitoring (to assess disease control)
  - Evidence and guidelines
  - Adverse events
  - Risk reduction (of adverse events such as falls)
  - Simplification/switches

**Benzodiazepines of Choice in the Elderly**
- LOT (Lorazepam)
- Oxazepam
- Temazepam

**Principles for Prescribing in the Elderly**
- CARED
  - Caution/Compliance
  - Age (adjust dosage for age)
  - Review regimen regularly
  - Educate
  - Discontinue unnecessary medications

**Geriatric Pearls.** Philadelphia: FA Davis Company, 1999

**Adverse drug reactions in the elderly may present as delirium, falls, fractures, urinary incontinence/retention or fecal incontinence/impaction**
Inappropriate Prescribing in the Elderly

Epidemiology
- The estimated prevalence of potentially inappropriate prescribing ranges from 12–40%.

Beers Criteria
- A list of medications to avoid in adults 65 yr and older due to safety concerns,
- Examples include long-acting benzodiazepines, strong anticholinergics, high-dose sedatives
- The elderly are also often under-treated (ACEI, ASA, β-blockers, thrombolytics, warfarin).

Common Medications

Table 12. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Enhancers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>donepezil</td>
<td>Aricept®</td>
<td>5-10 mg PO daily</td>
<td>Moderate to severe dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, caution in pulmonary disease, sick sinus syndrome, seizure disorder</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion</td>
<td>Reversible inhibition of acetylcholinesterase</td>
</tr>
<tr>
<td>galantamine</td>
<td>Reminyl®</td>
<td>8-12 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, caution in sick sinus syndrome, seizure disorder, pulmonary disease, low body weight</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion</td>
<td>Reversible inhibition of acetylcholinesterase</td>
</tr>
<tr>
<td>rivastigmine</td>
<td>Exelon®</td>
<td>1.5 mg PO daily (starting) up to 6 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, severe hepatic disease, caution in sick sinus syndrome, pulmonary disease, seizure disorder</td>
<td>N/V, diarrhea, anorexia, falls, hip fracture, increase need for pacemaker insertion</td>
<td>Acetylcholinesterase inhibition (reversible but very slow)</td>
</tr>
<tr>
<td>memantine</td>
<td>Ebixa® / Namenda® (Can) / U.S.)</td>
<td>5 mg PO daily (starting) up to 10 mg PO bid</td>
<td>Mild to moderate dementia of Alzheimer’s type</td>
<td>Known hypersensitivity, conditions that alkalize urine, caution in cardiovascular conditions</td>
<td>Agitation, fatigue, dizziness, headache, hypertension, constipation</td>
<td>NMDA-receptor antagonist</td>
</tr>
</tbody>
</table>

Laxatives

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>bran</td>
<td>All-Bran®</td>
<td>1 cup/d</td>
<td>Constipation</td>
<td></td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>psyllium</td>
<td>Metamucil®</td>
<td>1 tsp PO tid</td>
<td>Constipation, hypercholesterolemia</td>
<td>N/V, abdominal pain, obstruction</td>
<td>Bloating, flatus</td>
<td>Bulk-forming laxative</td>
</tr>
<tr>
<td>lactulose</td>
<td>Chronulac®</td>
<td>15-30 cc PO daily/bid</td>
<td>Constipation, hepatic encephalopathy, bowel evacuation following barium exam</td>
<td>Patients on low galactose diets</td>
<td>Abdominal pain, N/V</td>
<td>Hypermolar agent, lowers pH of colon to decrease blood ammonia levels</td>
</tr>
<tr>
<td>senna</td>
<td>Senokot® / Ex-lax® / Glytuss®</td>
<td>1-2 tabs PO daily or 10-15 cc syrup PO daily</td>
<td>Constipation</td>
<td>Abdominal pain, N/V</td>
<td>Cramps, gripeing, dependence</td>
<td>Stimulant laxative</td>
</tr>
<tr>
<td>bisacodyl</td>
<td>Dulcolax®</td>
<td>5-15 mg PO (10 mg PR)</td>
<td>Constipation</td>
<td>Ileus, obstruction, abdominal pain, N/V, severe dehydration</td>
<td>Cramps, pain, diarrhea</td>
<td>Stimulant laxative</td>
</tr>
</tbody>
</table>

Sleeping Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Brand Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>zopiclone</td>
<td>Imovane®</td>
<td>3.75 mg PO qhs (initially)</td>
<td>Insomnia</td>
<td>Known hypersensitivity, caution in myasthenia gravis, severe hepatic disease</td>
<td>Bitter taste, palpitations, vomiting, anorexia, sialorrhea, confusion, agitation, anxiety, tremor, sweating</td>
<td>Short-acting hypnotic (no tolerance effects)</td>
</tr>
<tr>
<td>temazepam</td>
<td>Restoril®</td>
<td>15 mg PO qhs</td>
<td>Short-term management of insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, sleep apnea</td>
<td>Drowsiness, dizziness, impaired coordination, hangover, lethargy, dependence</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
<tr>
<td>lorazepam</td>
<td>Ativan®</td>
<td>0.5 mg PO qhs (initially)</td>
<td>Anxiety, insomnia</td>
<td>Known hypersensitivity, myasthenia gravis, narrow-angle glaucoma</td>
<td>Dizziness, drowsiness, lethargy, dependence</td>
<td>Benzodiazepine: generalized CNS depression mediated by GABA</td>
</tr>
</tbody>
</table>

Note: Docusate has been shown to be ineffective for the prevention/treatment of constipation in the elderly.
Landmark Geriatric Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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</tr>
<tr>
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<td>Demonstrates that an interdisciplinary approach to elderly adults with a previous history of falls can significantly decrease the risk of further falls and limit functional impairment.</td>
</tr>
<tr>
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</tr>
</tbody>
</table>

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Elder Abuse

Falls

Frailty
Geriatric Pharmacology

Hazards of Hospitalization

Health Care Institutions

Health Status

Hypertension

Immunizations

Malnutrition

Palliative and End-of-Life Care

Physiology and Pathology of Aging

Pressure Ulcers
Gynecology

Dalia Bibr, Katie Bies, Christine Edwards, and James CM Wang, chapter editors Hasaan Chaudhry and Nardin Samuel, associate editors Alex Cressman and Shany Gertzbein, EBM editors Dr. Sari L. Kives, Dr. Ally Murji, and Dr. Fay Weisberg, staff editors

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Toronto Notes 2016
Basic Anatomy Review

A. EXTERNAL GENITALIA
• referred to collectively as the vulva
• blood supply: internal pudendal artery
• sensory innervation: pudendal nerve
• lymphatic drainage: inguinal nodes

B. VAGINA
• muscular canal extending from cervix to vulva, anterior to rectum and posterior to bladder
• lined by rugated, stratified-squamous epithelium
• upper vagina separated by cervix into anterior, posterior, and lateral fornices
• blood supply: vaginal branch of internal pudendal artery with anastamoses from uterine, inferior vesical, and middle rectal arteries

C. UTERUS
• thick walled, muscular organ between bladder and rectum, consisting of two major parts:
  • uterine corpus
  • cervix
• blood supply: uterine artery (branch of the internal iliac artery)
• supported by the pelvic diaphragm, the pelvic organs, and 4 paired sets of ligaments
• round ligaments: travel from anterior surface of uterus, through broad ligaments, and inguinal canals then terminate in the labia majora
• function: anteversion
• blood supply: Sampson’s artery (branch of uterine artery running through round ligament)
• uterosacral ligaments: arise from sacral fascia and insert into posterior inferior uterus
• function: mechanical support for uterus and contain autonomic nerve fibres
• cardinal ligaments: extend from lateral pelvic walls and insert into lateral cervix and vagina
• function: mechanical support, prevent prolapse
• broad ligaments: pass from lateral pelvic wall to sides of uterus; contain fallopian tube, round ligament, ovarian ligament, nerves, vessels, and lymphatics
• infundibulopelvic ligament: continuous tissue that connects ovary to pelvic wall
• contains the ovarian artery, ovarian vein, ovarian plexus, and lymphatic vessels
• position of the uterus
  • antverted (majority)
  • retroverted

Figure 1. Vulva and perineum

Figure 2. External genital organs

Acronyms
- β-hCG beta-human chorionic gonadotropin
- AFB alpha-fetoprotein
- AIS androgen insensitivity syndrome
- ASCUS atypical squamous cells of undetermined significance
- AUB abnormal uterine bleeding
- BMI body mass index
- BSO bilateral salpingo-oophorectomy
- BV bacterial vaginosis
- CAH congenital adrenal hyperplasia
- CMV cytomegalovirus
- Dbc dilatation and curettage
- DES diethylstilbestrol
- DHEA dihydroepiandrosterone
- DMPA depot-medroxyprogesterone acetate or Depo-Provera®
- DUB dysfunctional uterine bleeding
- DVT deep venous thrombosis
- EPC emergency postcoital contraception
- FSH follicle stimulating hormone
- GA gestational age
- GIFT gamete intrafallopian transfer
- GnRH gonadotropin-releasing hormone
- GDT gestational diabetes mellitus
- GTF gestational trophoblastic disease
- HERS heart and estrogen/progestin replacement study
- HMG human menopausal gonadotropin
- HPO hypothyroidism-pituitary-ovarian
- HPV human papillomavirus
- HRT hormone replacement therapy
- HSIL high grade squamous intraepithelial lesion
- HSV herpes simplex virus
- IBD inflammatory bowel disease
- ICSI intracytoplasmic sperm injection
- ITI immune thrombocytopenic purpura
- IU intraventricular device
- IUH intraventricular incontinence
- IVG intravenous drug use
- IVF in vitro fertilization
- IVM in vitro maturation
- JRA juvenile rheumatoid arthritis
- LDH lactate dehydrogenase
- LEEP loop electrosurgical excision procedure
- LH luteinizing hormone
- LHHRH luteinizing hormone releasing hormone
- LMP last menstrual period
- LN lymph node
- LMP last menstrual period
- LSIL low grade squamous intraepithelial lesion
- LVSLS lymphovascular space involvement
- MRRK Mayer-Rokitansky-Küster-Hauser
- NK natural killer
- OCP oral contraceptive pill
- OGTT oral glucose tolerance test
- PCOS polycystic ovarian syndrome
- PCL polymerase chain reaction
- PG prostaglandin
- PID pelvic inflammatory disease
- PADD premenstrual dysphoric disorder
- PMN polymorphonuclear neutrophils
- PMS premenstrual syndrome
- PRP rapid plasma reagin
- SSC squamous cell carcinoma
- SERM selective estrogen receptor modulators
- SHBG sex hormone binding globulin
- SHG sonohysterography
- SSRI selective serotonin reuptake inhibitors
- STI sexually transmitted infections
- TAH total abdominal hysterectomy
- TET tubal embryo transfer
- TH total hysterectomy
- TOT tension-free obturator tape
- TSH thyroid stimulating hormone
- TVT tension-free vaginal tape
- TZ transformation zone
- VDRI venereal disease research laboratory
- VEF vulvar intraepithelial neoplasia
- VTE venous thromboembolism
- vWD von Willebrand’s disease
- W/D withdrawal
- WHI Women’s Health Initiative
- ZIFT zygote intrafallopian transfer
D. FALLOPIAN TUBES
- 8-14 cm muscular tubes extending laterally from the uterus to ovary
- interstitial, isthmic, ampullary, and infundibular segments; terminates at fimbriae
- mesosalpinx: peritoneal fold that attaches fallopian tube to broad ligament
- blood supply: uterine and ovarian arteries

E. OVARIES
- consist of cortex with ova and medulla with blood supply
- supported by infundibulopelvic ligament (suspensory ligament of ovary)
- mesovarium: peritoneal fold that attaches ovary to broad ligament
- blood supply: ovarian arteries (branches off aorta), left ovarian vein (drains into left renal vein), right ovarian vein (drains into inferior vena cava)

Figure 4. Vascular supply

**Menstruation**

**Stages of Puberty**
- see Pediatrics, P31
- adrenarche: increase in secretion of adrenal androgens; usually precedes gonadarche by 2 yr
- gonadarche: increased secretion of gonadal sex steroids; ~age 8 yr
- thelarche: breast development
- pubarche: pubic and axillary hair development
- menarche: onset of menses, usually following peak height velocity and/or 2 yr following breast budding
**Menstrual Cycle**

### Characteristics
- Menarche: 10-15 yr
- Average: 12.2 yr
- Entire cycle: 28 ± 7 d with bleeding for 1-6 d
- 25-80 mL blood loss per cycle

### Estrogen
- **ESTROGEN** is the main hormone in the follicular/proliferative phase and is stimulated by FSH. As the level increases it acts negatively on FSH. The majority of estrogen is secreted by the dominant follicle.

#### Estrogen effects
- On the follicles in the ovaries
  - Reduces atresia
- On the endometrium
  - Proliferation of glandular and stromal tissue
- On all target tissues
  - Decreases E receptors

### Progesterone
- **PROGESTERONE** is the main hormone in the luteal/secretory phase and is stimulated by LH. Increased progesterone acts negatively on LH and is secreted by the corpus luteum (remnant of dominant follicle).

#### Progesterone effects
- On the endometrium
  - Cessation of mitoses (stops building endometrium up)
  - “Organization” of glands (initiates secretions from glands)
  - Inhibits macrophages, interleukin-8, and enzymes from degrading endometrium
- On all target tissues
  - Decrease E receptors (the “anti-estrogen” effect)
  - Decrease P receptors

---

**Figure 5. Events of the normal menstrual cycle**

- **FOLLICULAR/PROLIFERATIVE PHASE (Variable Duration)**
  - Early: ↓ E and ↓ P (from end of previous cycle)
  - Mid: ↑ FSH acts on ovarian granulosa cells
  - Late: Growing follicles continue to secrete E

- **LUTEAL/SECRETORY PHASE (Fixed Duration - 14 days)**
  - Early-Mid: Sudden switch from negative to positive feedback (E and P now ↑ FSH & LH)
  - Late: Switch back to negative feedback

- **Ovulation**
  - Early-Mid: ↑ LH pulse amplitude (LH surge)
  - Late: ↓ LH

- **HPO Axis**
  - Early: ↓ E and ↓ P (from end of previous cycle)
  - Mid: ↑ FSH pulse frequency
  - Late: ↓ LH pulse frequency

- **Hormones**
  - Early: ↓ E from follicles (ovary)
  - Mid: ↑ LH from follicles (ovary)
  - Late: ↓ LH from corpus luteum

- **Feedback on HPO Axis**
  - Early: Negative feedback E → ↓ FSH, ↓ LH
  - Mid: ↓ LH pulse frequency
  - Late: ↓ LH pulse frequency

- **Ovaries**
  - Early: ↑ follicular growth in 3-30 follicles
  - Mid: ↓ LH from corpus luteum
  - Late: ↓ LH from corpus luteum

- **Endometrium**
  - Early: Menses from P withdrawal
  - Mid: E builds up endometrium
  - Late: P stabilizes endometrium

- **Cervical Mucus**
  - Early: Cervical mucus: Clear, ↑ amount, Spinnbarkeit 8-10 cm, more stringy
  - Mid: Opaque, scant amount, Spinnbarkeit 1-2 cm
**Premenstrual Syndrome**

- **synonyms:** “ovarian cycle syndrome,” “menstrual molimina” (moodiness)

**Etiology**
- multifactorial: not completely understood; genetics likely play a role
- CNS-mediated neurotransmitter interactions with sex steroids (progesterone, estrogen, and testosterone)
- serotonergic dysregulation – currently most plausible theory

**Diagnostic Criteria for Premenstrual Syndrome**
- at least one affective and one somatic symptom during the 5 d before menses in each of the three prior menstrual cycles
  - affective: depression, angry outbursts, irritability, anxiety, confusion, social withdrawal
  - somatic: breast tenderness, abdominal bloating, headache, swelling of extremities
- symptoms relieved within 4 d of onset of menses
- symptoms present in the absence of any pharmacologic therapy, drug or alcohol use
- symptoms occur reproducibly during 2 cycles of prospective recording
- patient suffers from identifiable dysfunction in social or economic performance

**Treatment**
- goal: symptom relief
- psychological support
- diet SUPPLEMENTS
  - avoid sodium, simple sugars, caffeine, and alcohol
  - calcium (1,200-1,600 mg/d), magnesium (400-800 mg/d), vitamin E (400 IU/d), vitamin B6
- medications
  - NSAIDs for discomfort and pain
  - spironolactone for fluid retention: used during luteal phase
  - SSRIs: used during luteal phase x 14 d or continuously
  - OCP: primarily beneficial for physical/somatic symptoms
  - danazol: an androgen that inhibits the pituitary-ovarian axis
  - GnRH agonists if PMS is severe and unresponsive to treatment (may use prior to considering definitive treatment with BSO)
- mind body approaches
  - regular aerobic exercise
  - cognitive behavioural therapy
  - relaxation, light therapy biofeedback, and guided imagery
- herbal remedies (variable evidence)
  - evening primrose oil, black cohosh, St. John’s wort, kava, ginkgo, agnus castus fruit extract
- BSO if symptoms severe

**Premenstrual Dysphoric Disorder**

**Definition**
- official diagnosis in the DSM-5
- described as a more severe form of PMS with specific diagnostic criteria
- treatment with SSRIs (first line), and Yaz OCP (highly effective)
Abnormal Uterine Bleeding

- see Disorders of Menstruation, GY10
- menstrual bleeding should be evaluated by ascertaining: frequency/regularity of menses, duration, volume of flow, affects on quality of life and timing (inter or premenstrual or breakthrough)
- classified as
  - regular: cycle to cycle variability of <20 d
  - irregular: cycle to cycle variability of ≥20 d
  - heavy menstrual bleeding: ≥80 cc of blood loss per cycle or ≥8 d of bleeding per cycle or bleeding that significantly affects quality of life
  - postmenopausal bleeding: any bleeding that presents >1 yr after menopause; must rule out endometrial cancer

Dysmenorrhea

- see Disorders of Menstruation, GY13
- primary/idiopathic
- secondary (acquired)
  - endometriosis
  - adenomyosis
  - uterine polyps
  - uterine anomalies (e.g. non-communicating uterine horn)
  - leiomyoma
  - intrauterine synechiae
  - ovarian cysts
  - cervical stenosis
  - imperforate hymen, transverse vaginal septum
  - pelvic inflammatory disease
  - IUD (copper)
  - foreign body

Vaginal Discharge/Pruritus

- see Gynecological Infections, GY25
- physiologic discharge and cervical mucus production
- non-physiologic
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - systemic: toxic shock syndrome, Crohn's disease, collagen disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)
Pelvic Pain

- **Acute**
  - Gynecological
  - Non-gynecological
- **Chronic**
  - Gynecological
  - Chronic PID
  - Endometriosis
  - Adenomyosis
  - Adhesions
  - Dysmenorrhea
  - Pelvic congestion syndrome
  - Ovarian remnant syndrome
  - Fibroid (rare)
  - Uterine prolapse (rare)
- **Non-gynecological**
  - Referred pain
  - Urinary retention
  - Urethral syndrome
  - Interstitial cystitis
  - GI neoplasm
  - IBS
  - IBD
  - Constipation
  - Partial bowel obstruction
  - Diverticulitis
  - Hernia formation
  - Nerve entrapment
  - Sexual/physical/psychological abuse
  - Depression
  - Anxiety
  - Somatization

- **Adnexal**
  - Mittelschmerz
  - Ruptured ovarian cyst
  - Ruptured ectopic pregnancy
  - Hemorrhage into cyst/neoplasm
  - Ovarian/tubal torsion

- **Uterine**
  - Fibroid degeneration
  - Torsion of pedunculated fibroid
  - Pyometra/hematometra
  - Endometritis

- **Gastrointestinal**
  - Appendicitis
  - Mesenteric adenitis
  - Diverticulitis
  - IBD
  - Renal colic

**Note:** 20% of chronic pelvic pain patients have a history of previous sexual abuse/assault; remember to ask about it.

Figure 7. Approach to pelvic pain

Pelvic Mass

- **Ovarian**
  - Functional Cysts (always benign)
    - Corpus luteum cyst
    - Follicular cyst
    - Theca lutein cyst
    - Hemorrhagic cyst
  - Neoplasm
    - Benign (most common in >40 yr)
      - Dermoid cyst
    - Malignant (most common in <20 yr)
      - Epithelial cell
  - Other
    - PCOS
    - Endometrioma
    - Tube-ovarian abscess
    - Luteoma of pregnancy

- **Neoplasms**
  - Benign
    - Corpus luteum cyst
    - Follicular cyst
    - Theca lutein cyst
    - Hemorrhagic cyst
  - Malignant
    - Most common (mesonephric and paramesonephric cysts)
    - Inflammation, cysts (mesonephric, paramesonephric)
    - Malignancy
    - Tubo-ovarian abscess (PID)

- **Other**
  - Gynecological
    - Ectopic pregnancy
    - Pelvic adhesions (resulting in fluid entrapment)
    - Paratubal cysts
    - Pyosalpinx/Hydrosalpinx
    - Primary fallopian tube neoplasms
  - Gastrointestinal
    - Appendiceal abscess
    - Diverticular abscess
    - Diverticulosis, diverticulitis
    - Carcinoma of rectum/colon
  - Genitourinary
    - Distended bladder
    - Pelvic kidney
    - Carcinoma of bladder
  - Lymphoma

Figure 8. Differential diagnosis of pelvic mass
**Dyspareunia**

![Dyspareunia Diagram](image)

**First and Second Trimester Bleeding**

**Approach to the Patient with Bleeding in T1/T2**

**History**
- risk factors for ectopic pregnancy (see Ectopic Pregnancy, GY21)
- previous spontaneous abortion
- recent trauma
- characteristics of the bleeding (including any tissue passed)
- characteristics of the pain (cramping pain suggests spontaneous abortion)
- history of coagulopathy
- gynecological/obstetric history
- fatigue, dizziness, syncopal episodes due to hypovolemia, fever (may be associated with septic abortion)

**Physical**
- vitals (including orthostatic changes)
- abdomen (symphysis fundal height, tenderness, presence of contractions)
- perineum (signs of trauma, genital lesions)
- speculum exam (cervical os open or closed, presence of active bleeding/clots/tissue)
- pelvic exam (uterine size, adnexal mass, uterine/adnexal tenderness)

**Investigations**
- \(\beta\)-hCG (lower than expected for GA in spontaneous abortion, ectopic pregnancy)
- U/S (confirm intrauterine pregnancy and fetal viability)
- CBC
- group and screen

**Treatment**
- IV resuscitation for hemorrhagic shock
- treat the underlying cause

**Common Investigations and Procedures**

**Imaging**

**Ultrasound (U/S)**
- transabdominal or transvaginal U/S is the imaging modality of choice for pelvic structures
- transvaginal U/S provides better resolution of uterus and adnexal structures
  - detects early pregnancy if \(\beta\)-hCG \(\geq\) 1,500 (\(\beta\)-hCG must be \(\geq\) 6,500 for transabdominal U/S)
  - may be used to identify pelvic pathology
  - identify ectopic pregnancy, intrauterine pregnancy
  - assess uterine, adnexal, cul-de-sac, ovarian masses (e.g. solid or cystic)
  - determine endometrial thickness, locate/characterize fibroids
  - monitor follicles during assisted reproduction
  - assess endometrial lining in postmenopausal women

Every woman of childbearing age presenting to ER with abdominal or pelvic pain should have \(\beta\)-hCG measured
**Endometrial Biopsy**

- performed in the office using an endometrial suction curette (pipelle) guided through the cervix to aspirate fragments of endometrium
  - pre-treatment with misoprostol (Cyteoc®) if nulliparous or postmenopausal
- more invasive procedure (D&C) may be done in the office or operating room ± hysteroscopy
- indications
  - AUB/PMB
  - cancer screening (e.g. following specific cervical cytology results (i.e. AGUS) or in high-risk women)

**Hysterectomy**

Indications
- uterine fibroids
- endometriosis, adenomyosis
- uterine prolapse
- pelvic pain
- AUB
- cancer (endometrium, ovaries, fallopian tubes, cervix)

Complications
- general anesthetic
- bleeding
- infection
- injury to other organs (ureter, bladder, rectum)
- loss of ovarian function (if ovaries removed, iatrogenic menopause)

Approaches
1. vaginal vs. abdominal
   - indications for vaginal approach: mobile uterus, uterine size <12 wk
   - advantages of vaginal approach: less pain, faster recovery time, allows for simultaneous repair of rectocele/cystocele/enterocele, improved aesthetics
2. open vs. laparoscopic-assisted
   - advantages of laparoscopy: less pain, faster recovery, improved aesthetics, shorter hospital stay
   - unless contraindicated or unavailable laparoscopic hysterectomy is the standard of care
3. robotic
   - similar advantages to laparoscopy
   - more dexterous

**Table 1. Classification of Hysterectomy**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Tissues Removed</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subtotal Hysterectomy</td>
<td>Uterus</td>
<td>Inaccessible cervix (e.g. adhesions) Patient choice/preference</td>
</tr>
<tr>
<td>Total Hysterectomy (extrafascial</td>
<td>Uterus, cervix, uterine artery ligated at uterus</td>
<td>Uterine fibroids Endometriosis Adenomyosis Menorrhagia DUB</td>
</tr>
<tr>
<td>simple hysterectomy/type 1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Hysterectomy (extrafascial</td>
<td>Uterus, cervix, uterine artery ligated at uterus</td>
<td>Endometrial cancer Malignant adnexal masses &gt;45 yr old Consider for endometriosis</td>
</tr>
<tr>
<td>simple hysterectomy/type 1) +</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral Salpingo-Oophorectomy (TAH/BSO)</td>
<td>Uterus, cervix, uterine artery ligated at uterus</td>
<td></td>
</tr>
<tr>
<td>Modifed Radical Hysterectomy (type 2)</td>
<td>Uterus, cervix, proximal 1/3 parametria, uterine artery ligated medial to the ureter, mid point of uterosacral ligaments and upper 1-2 cm vagina</td>
<td>Cervical cancer (up to stage IIB)</td>
</tr>
<tr>
<td>Radical Hysterectomy (type 3)</td>
<td>Uterus, cervix, upper 1/3-1/2 vagina, entire parametria, uterine artery ligated at its origin from internal iliac artery, uterosacral ligament at most distal attachment (rectum)</td>
<td>Cervical cancer</td>
</tr>
</tbody>
</table>
Disorders of Menstruation

Amenorrhea

Differential Diagnosis of Amenorrhea

Table 2. Differential Diagnosis of Primary Amenorrhea

<table>
<thead>
<tr>
<th>With Secondary Sexual Development</th>
<th>Without Secondary Sexual Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal breast and pelvic development</td>
<td>Normal breast, abnormal uterine development</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>PCOS</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Hypothalamic dysfunction</td>
</tr>
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<td>Hypothyroidism</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>PCOS</td>
</tr>
</tbody>
</table>

Table 3. Differential Diagnosis of Secondary Amenorrhea

<table>
<thead>
<tr>
<th>With Hyperandrogenism</th>
<th>Without Hyperandrogenism</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCOS</td>
<td>Hypergonadotropic hypogonadism (i.e. premature ovarian failure: high FSH, low estradiol)</td>
</tr>
<tr>
<td>Autonomous hyperandrogenism (androgen secretion independent of the HPO axis)</td>
<td>• Idiopathic</td>
</tr>
<tr>
<td>• Ovarian: tumour, hyperthecosis</td>
<td>• Autoimmune: type 1 DM, autoimmune thyroid disease, Addison’s disease</td>
</tr>
<tr>
<td>• Adrenal androgen-secreting tumour</td>
<td>• Iatrogenic: cyclophosphamide drugs, radiation</td>
</tr>
<tr>
<td>Late onset or mild congenital adrenal hyperplasia (rare)</td>
<td>Hyperprolactinemia</td>
</tr>
<tr>
<td>Endocrinopathies: most commonly hyper or hypothyroidism</td>
<td>Hypergonadotropic hypogonadism (low FSH):</td>
</tr>
<tr>
<td>• Pituitary compression or destruction: pituitary adenoma, craniopharyngioma, lymphocytic hypophysitis, infiltration (sarcoidosis), head injury, Sheehan’s syndrome</td>
<td>• Pituitary failure (Kallman syndrome, head injury, pituitary adenoma, etc.)</td>
</tr>
<tr>
<td>Functional hypothalamic amenorrhea (often related to stress excessive exercise and/or anorexia)</td>
<td>Acquired</td>
</tr>
</tbody>
</table>

Investigations

Figure 10. Diagnostic approach to amenorrhea
• β-hCG, hormonal workup (TSH, prolactin, FSH, LH, androgens, estradiol)
• progesterone challenge to assess estrogen status
  ▪ medroxyprogesterone acetate (Provera) 10 mg PO OD for 10-14 d
  ▪ any uterine bleed within 2-7 d after completion of Provera is considered to be a positive test/withdrawal bleed
  ▪ withdrawal bleed suggests presence of adequate estrogen to thicken the endometrium; thus withdrawal of progesterone results in bleeding
  ▪ if no bleeding occurs, there may be inadequate estrogen (hypoestrogenism), excessive androgens, or progesterones (decidualization)
• karyotype: indicated if premature ovarian failure or absent puberty
• U/S to confirm normal anatomy, identify PCOS

### Treatment

#### Table 4. Management of Amenorrhea

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1º AMENORRHEA</strong></td>
<td></td>
</tr>
</tbody>
</table>
| Androgen insensitivity syndrome | • Gonadal resection after puberty  
|                               | • Psychological counselling  
|                               | • Creation of neo-vagina                                                |
| Anatomical                    | • Surgical management                                                    |
| • Imperforate hymen           |                                                                           |
| • Transverse vaginal septum   |                                                                           |
| • Cervical agenesis           |                                                                           |
| Müllerian dysgenesis (MRKH syndrome) | • Psychological counselling  
|                               | • Creation of neo-vagina with dilation  
|                               | • Diagnostic study to confirm normal urinary system and spine            |
| **2º AMENORRHEA**             |                                                                           |
| Uterine defect                | • Evaluation with hysterosalpingography or sonohysterography             |
| • Asherman’s syndrome         | • Hysteroscopy; excision of synechiae                                   |
| HP-axis dysfunction           | • Identify modifiable underlying cause                                   |
| Premature ovarian failure     | • Combined OCP to decrease risk of osteoporosis, maintain normal vaginal and breast development (NOT proven to work) |
| Hyperprolactinemia            | • MRI/CT head to rule out lesion                                         |
| • Screen for DM, hypothyroidism, hypoparathyroidism, hypocorticolism | • If no demonstrable lesions by MRI                                     |
| • Hormonal therapy with estrogen + progestin to decrease risk of osteoporosis; can use OCP | • Bremocriptine, cabergoline if fertility desired                        |
| Polycystic ovarian syndrome   | • Demonstrable lesions by MRI: surgical management                      |
|                               | • See Polycystic Ovarian Syndrome, GY25                                 |

### Abnormal Uterine Bleeding

**Figure 11. Diagnostic approach to abnormal uterine bleeding**

**Approach**

- is it regular?
  ▪ predictable vs. unpredictable cycle
- is it heavy
- is it structural?
  ▪ PALM
- is it non-structural?
  ▪ COEIN
### Table 5. AUB – Etiologies, Investigations, and Management

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRUCTURAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyps (AUB-P)</td>
<td>Transvaginal Sonography</td>
<td>Polypectomy (triage based on symptomatic, polyp size, histopathology &amp; patient age)</td>
</tr>
<tr>
<td></td>
<td>Saline Infusion Sonohysterography</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>Adenomyosis (AUB-A)</td>
<td>Transvaginal Sonography</td>
<td>see Adenomyosis, GY15</td>
</tr>
<tr>
<td></td>
<td>MRI</td>
<td></td>
</tr>
<tr>
<td>Leiomyoma (AUB-L)</td>
<td>Transvaginal Sonography</td>
<td>see Leiomyomatosis (fibroids), GY15</td>
</tr>
<tr>
<td>• Submuosal (AUB-LSM)</td>
<td>Saline Infusion Sonohysterography</td>
<td></td>
</tr>
<tr>
<td>• Other (AUB-LO)</td>
<td>Diagnostic Hysteroscopy</td>
<td></td>
</tr>
<tr>
<td>Malignancy &amp; Hyperplasia (AUB-M)</td>
<td>Transvaginal Sonography</td>
<td>Endometrial Biopsy - consider biopsy in women &gt;40 yr to exclude endometrial cancer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dependent on diagnosis</td>
</tr>
<tr>
<td><strong>NON-STRUCTURAL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coagulopathy (AUB-C)</td>
<td>CBC, coagulation profile (especially in adolescents), von Willebrand Factor, Fibrinogen, Factor VIII</td>
<td>Dependent on diagnosis</td>
</tr>
<tr>
<td>Ovulatory dysfunction (AUB-D)</td>
<td>Bloodwork: β-hCG, ferritin, prolatin, FSH, LH, serum androgens (free testosterone, DHEA), progesterone, 17-hydroxy progesterone, TSH, FT4 pelvic ultrasound</td>
<td>see Infertility, GY23</td>
</tr>
<tr>
<td>Endometrial (AUB-E)</td>
<td>Endometrial Biopsy</td>
<td>see Endometriosis, GY13</td>
</tr>
<tr>
<td>Iatrogenic (AUB-I)</td>
<td>Transvaginal Sonography (rule out forgotten IUD)</td>
<td>Remove offending agent</td>
</tr>
<tr>
<td></td>
<td>Review OCP/HRT use</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Review meds (especially neuroleptic use)</td>
<td></td>
</tr>
<tr>
<td><strong>Not yet classified (AUB-N)</strong></td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

*Ferrous gluconate 300 mg PO TID will raise Hb 10 points per wk*

### Treatment
- resuscitate patient if hemodynamically unstable
- treat underlying disorders
  - if anatomic lesions and systemic disease have been ruled out, consider DUB
- medical
  - mild DUB
  - NSAIDs
  - anti-fibrinolytic (e.g. Cyklokapron*) at time of menses
  - combined OCP
  - progestins (Provera*) on first 10-14 d of each month or every 3 mo if oligomenorrheic
  - Mirena* IUD
  - danazol
  - acute, severe DUB
    - replace fluid losses, consider admission
    - a) estrogen (Premarin*) 25 mg IV q4h x 24 h with Gravol* 50 mg IV/PO q4h or anti-fibrinolytic (e.g. Cyklokapron*) 10 mg/kg IV q8h
    - b) any OCP with minimum 50 µg estradiol 1 tab PO q4h x 24 h with Gravol* 50 mg IV/PO q4h
      - taper to 1 tab tid x 2 d → bid x 2 d → OD
    - after (a) or (b), maintain patient on monophasic OCP for next several months or consider alternative medical treatment
  - clomiphene citrate
    - consider in patients who are anovulatory and who wish to get pregnant
- surgical
  - endometrial ablation; consider pretreatment with danazol or GnRH agonists
  - if finished childbearing
  - repeat procedure may be required if symptom reoccur especially if <40 yr
  - hysterectomy: definitive treatment

---

**Dysfunctional Uterine Bleeding**
Abnormal bleeding not attributable to organic (anatomic/systemic) disease
DUB is a diagnosis of exclusion
Anovulatory AUB often used synonymously with DUB

AUB in women >40 yr requires an endometrial biopsy to rule out cancer even if known to have fibroids

Determine if patient is hemodynamically stable prior to any other task
### Dysmenorrhea

**Etiology**
- see Differential Diagnoses of Common Presentations, GY6

**Table 6. Comparison of Primary and Secondary Dysmenorrhea**

<table>
<thead>
<tr>
<th></th>
<th>Primary Dysmenorrhea</th>
<th>Secondary Dysmenorrhea</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Features</strong></td>
<td>Menstrual pain in absence of organic disease</td>
<td>Menstrual pain due to organic disease</td>
</tr>
<tr>
<td></td>
<td>Begins 6 mo-2 yr after menarche (once ovulatory cycles established)</td>
<td>Usually begins in women who are in their 20s, worsens with age May improve temporarily after childbirth</td>
</tr>
<tr>
<td><strong>Signs and Symptoms</strong></td>
<td>Colicky pain in abdomen, radiating to the lower back, labia, and inner thighs beginning hours before onset of bleeding and persisting for hours or days (48-72 h) Associated symptoms: N/V, altered bowel habits, headaches, fatigue (prostaglandin-associated)</td>
<td>Associated dyspareunia, abnormal bleeding, infertility</td>
</tr>
<tr>
<td><strong>Diagnosis</strong></td>
<td>Associated dyspareunia, abnormal bleeding, infertility Rule out underlying pelvic pathology and confirm cyclic nature of pain</td>
<td>Bimanual exam: uterine or adnexal tenderness, fixed uterine retroflexion, uterosacral nodularity, pelvic mass, or enlarged irregular uterus (findings are rare in women &lt;20 yr) U/S, laparoscopy and hysteroscopy may be necessary to establish the diagnosis Screening for infections (vaginal and cervical cultures) and Papanicolaou smear may be required</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>PG synthetase inhibitors (e.g. Anaprox®): should be started before onset of pain OCP: suppress ovulation/reduce menstrual flow</td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>

### Endometriosis

**Etiology**
- not fully understood
- proposed mechanisms (combination likely involved)
  - retrograde menstruation (Sampson’s theory)
    - seeding of endometrial cells by trans tubal regurgitation during menstruation
    - endometrial cells most often found in dependent sites of the pelvis
  - immunologic theory: altered immunity may limit clearance of transplanted endometrial cells from pelvic cavity (may be due to decreased NK cell activity)
  - metaplasia of coelomic epithelium
    - undefined endogenous biochemical factor may induce undifferentiated peritoneal cells to develop into endometrial tissue
  - extrapelvic disease may be due to aberrant vascular or lymphatic dissemination of cells
    - e.g. ovarian endometriosis may be due to direct lymphatic flow from uterus to ovaries

**Epidemiology**
- incidence: 15-30% of pre-menopausal women
- mean age at presentation: 25-30 yr
- regresses after menopause

**Risk Factors**
- family history (7-10x increased risk if affected 1st degree relative)
- obstructive anomalies of the genital tract (earlier onset) – resolve with treatment of anomaly
- nulliparity
- age >25 yr

**Sites of Occurrence**
- ovaries: 60% patients have ovarian involvement
- broad ligament, vesicoperitoneal fold
- peritoneal surface of the cul-de-sac, uterosacral ligaments
- rectosigmoid colon, appendix
- rarely may occur in sites outside abdomen/pelvis, including lungs

**Endometriosis is classified according to a scoring system standardized by the American Society for Reproductive Medicine; score is based on location and extent of disease**

**Endometriosis**
- The presence of endometrial tissue (glands and stroma) outside of the uterine cavity

**Endometrioma**
- Endometriotic cyst on surface of ovary

**Differential Diagnoses**
- Chronic PID, recurrent acute salpingitis
- Hemorrhagic corpus luteum
- Benign/malignant ovarian neoplasm
- Ectopic pregnancy

**Recurrence Rates**
- Medical therapy: 30-50%
- Conservative surgery: 14-40%
Clinical Features

- may be asymptomatic and can occur with one of 3 presentations

1. **pain**
   - menstrual symptoms
   - cyclic symptoms due to growth and bleeding of ectopic endometrium, usually precede menses (24-48 h) and continue throughout and after flow
   - secondary dysmenorrhea
   - sacral backache with menses
   - pain may eventually become chronic, worsening perimenstrually
   - deep dyspareunia
   - bowel and bladder symptoms
     - frequency, dysuria, hematuria
   - cyclic diarrhea/constipation, hematochezia, dyschezia (suggestive of deeply infiltrating disease)

2. **infertility**
   - 30-40% of patients with endometriosis will be infertile
   - 15-30% of those who are infertile will have endometriosis

3. **mass (endometrioma)**
   - ovarian mass can present with any of above symptoms or be asymptomatic
   - physical
     - tender nodularity of uterine ligaments and cul-de-sac felt on rectovaginal exam
     - fixed retroversion of uterus
     - firm, fixed adnexal mass (endometrioma)
     - physical findings not present in adolescent population

Investigations

- definitive diagnosis requires
  - direct visualization of lesions typical of endometriosis at laparoscopy
  - biopsy and histologic exam of specimens (2 or more of: endometrial epithelium, glands, stroma, hemosiderin-laden macrophages)

- laparoscopy
  - mulberry spots: dark blue or brownish-black implants on the uterosacral ligaments, cul-de-sac, or anywhere in the pelvis
  - endometrioma: "chocolate" cysts on the ovaries
  - 'powder-burn' lesions on the peritoneal surface
  - early white lesions and clear blebs
  - peritoneal "pockets"
- CA-125
  - may be elevated in patients with endometriosis

Treatment

- surgical: confirmation of disease is NOT required prior to starting medical management. Asymptomatic endometriosis does not require treatment. Management depends on certainty of the diagnosis, severity of symptoms, extent of disease, desire for future fertility, and impact to GI/GU systems (e.g. intestinal obstruction)
  - medical
    - NSAIDs (e.g. naproxen sodium – Anaprox®)
    - 1st line
      - cyclic/continuous estrogen-progestin (OCP)
      - progestin (IM medroxyprogesterone (Depo-Provera®) or oral dienogest (Visanne®)
      - Mirena® IUS
    - 2nd line
      - 2nd line: GnRH-a example: leuprolide (Lupron®): GnRH agonist (suppresses pituitary)
        - side effects: hot flashes, vaginal dryness, reduced libido
        - can use ≥12 mo with add-back progestin or estrogen
        - danazol (Danocrine®): weak androgen
          - side effects: weight gain, fluid retention, acne, hirsutism, voice change
  - surgical
    - conservative laparoscopy using laser, electrocautery ± laparotomy
    - ablation/resection of implants, lysis of adhesions, ovarian cystectomy of endometriomas
    - definitive: bilateral salpingo-oophorectomy ± hysterectomy
  - ± follow-up with medical treatment for pain control not shown to impact on preservation of fertility
  - best time to become pregnant is immediately after conservative surgery
Adenomyosis

• synonym: “endometriosis interna” (uterine wall may be diffusely involved)

Epidemiology
• 15% of females >35 yr old; found in 20-40% of hysterectomy specimens
• mean age at presentation: 40-50 yr old (older age group than seen in endometriosis)
• adenomyosis is a common histologic finding in asymptomatic patients

Clinical Features
• often asymptomatic
• menorrhagia, secondary dysmenorrhea, pelvic discomfort
• dyspareunia, dyschezia
• uterus symmetrically bulky, usually <14 cm, mobility not restricted, no associated adnexal pathology
• Halban sign: tender, softened uterus on premenstrual bimanual exam

Investigations
• clinical diagnosis
• U/S or MRI can be helpful
• endometrial sampling to rule out other pathology

Treatment
• iron supplements as necessary
• analgesics, NSAIDs
• OCP, medroxyprogesterone (Depo-Provera®)
• GnRH agonists (e.g. leuprolide)
• Mirena® IUS
• low dose danazol 100-200 mg PO OD (trial x 4 mo)
• definitive: hysterectomy (no conservative surgical treatment)

Leiomyomata (Fibroids)

Epidemiology
• diagnosed in approximately 40-50% of pre-menopausal women >35 yr
• more common in African Americans, where they are also larger and occur at earlier age
• common indication for major surgery in females
• minimal malignant potential (1:1,000)
• typically regress after menopause; enlarging fibroids in a postmenopausal woman should prompt consideration of malignancy
  ▪ 50% of leiomyosarcomas originate from within fibroids

Pathogenesis
• estrogen stimulates monoclonal smooth muscle proliferation
• progesterone stimulates production of proteins that inhibit apoptosis
• degenerative changes (occur when tumour outgrows blood supply)
  ▪ fibroids can degenerate, become calcified, have sarcomatous component or obtain parasitic blood supply

Clinical Features
• majority asymptomatic (60%), often discovered as incidental finding on pelvic exam or U/S
• abnormal uterine bleeding (30%): dysmenorrhea, menorrhagia
• pressure/bulk symptoms (20-50%)
  ▪ pelvic pressure/heaviness
  ▪ increased abdominal girth
  ▪ urinary frequency and urgency
  ▪ acute urinary retention (extremely rare but surgical emergency!)
  ▪ constipation, bloating (rare)
• acute pelvic pain
  ▪ fibroid degeneration
  ▪ fibroid torsion (pedunculated subserosal)
• infertility, recurrent pregnancy loss
• pregnancy complications (potential enlargement and increased pain, obstructed labour, difficult C-section)
Investigations

- bimanual exam: uterus asymmetrically enlarged, usually mobile
- CBC: anemia
- U/S: to confirm diagnosis and assess location of fibroids
- sonohysterogram: useful for differentiating endometrial polyps from submucosal fibroids, or if intracavitary growth
- endometrial biopsy to rule out uterine cancer for abnormal uterine bleeding (especially if age >40 yr)
- occasionally MRI is used for pre-operative planning (e.g. before myomectomy)

Treatment

- only if symptomatic, rapidly enlarging, menorrhagia, menometrorrhagia, or intracavitary fibroids
- treat anemia if present
- conservative approach (watch and wait) if
  - symptoms absent or minimal
  - fibroids <6-8 cm or stable in size
  - not submucosal (submucosal fibroids are more likely to be symptomatic)
  - currently pregnant due to increased risk of bleeding (follow-up U/S if symptoms progress)
- medical approach to treat AUB-L
  - antiprostaglandins (ibuprofen, other NSAIDs)
  - tranexamic acid (Cyklokapron*)
  - OCP/Depo-Provera*
  - GnRH agonist: leuprolide (Lupron*), danazol (Danocrine*)
    - short-term use only (6 mo)
    - often used pre-myomectomy or pre-hysterectomy to reduce fibroid size
    - reduced bleeding
  - ulipristal acetate: a partial progesterone receptor agonist
- interventional radiology approach
  - uterine artery embolization (occludes both uterine arteries) → shrinks fibroids by 50% at 6 mo; improves menorrhagia in 90% of patients within 1-2 mo; not an option in women considering childbearing
- surgical approach
  - myomectomy (hysteroscopic, transabdominal, or laparoscopic): preserves fertility
  - hysterectomy (see Hysterectomy, GY9)
  - note: avoid operating on fibroids during pregnancy (due to ↑ vascularity and potential pregnancy loss); expectant management usually best

Contraception

- see Family Medicine, FM20

Table 7. Classification of Contraceptive Methods

<table>
<thead>
<tr>
<th>Type</th>
<th>Effectiveness (Perfect Use, Typical Use)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Physiological</strong></td>
<td></td>
</tr>
<tr>
<td>Withdrawal/coitus interruptus</td>
<td>77%</td>
</tr>
<tr>
<td>Rhythm method/calendar/mucus/symptothermal</td>
<td>98%, 76%</td>
</tr>
<tr>
<td>Lactational amenorrhea</td>
<td>98% (first 6 mo postpartum)</td>
</tr>
<tr>
<td>Chance – no method used</td>
<td>10%</td>
</tr>
<tr>
<td>Abstinence of all sexual activity</td>
<td>100%</td>
</tr>
<tr>
<td><strong>Barrier Methods</strong></td>
<td></td>
</tr>
<tr>
<td>Condom alone</td>
<td>98%, 85%</td>
</tr>
<tr>
<td>Spermicide alone</td>
<td>82%, 71%</td>
</tr>
<tr>
<td>Sponge – Parous</td>
<td>80%, 68%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 84%</td>
</tr>
<tr>
<td>Diaphragm with spermicide</td>
<td>94%, 84%</td>
</tr>
<tr>
<td>Female condom</td>
<td>95%, 79%</td>
</tr>
<tr>
<td>Cervical cap – Parous</td>
<td>74%, 68%</td>
</tr>
<tr>
<td>– Nulliparous</td>
<td>91%, 84%</td>
</tr>
</tbody>
</table>

The effect of pregnancy on fibroid size is variable

Ulipristal Acetate vs. Leuprolide Acetate for Uterine Fibroids

NEJM 2012;366:421-432

Study: Phase III, double-blind RCT of the efficacy and side-effect profile of ulipristal acetate versus those of leuprolide acetate for the treatment of symptomatic uterine fibroids before surgery.

Outcomes: Control of uterine bleeding at week 13 was the primary outcome. Secondary outcomes included bleeding pattern, amenorrhea, changes in fibroid/uterine volume, and global pain score.

Patients: 307 premenopausal women with symptomatic fibroids and excessive uterine bleeding were randomly assigned to oral ulipristal acetate (5 mg or 10 mg) or intramuscular injections of leuprolide acetate.

Results: Control of bleeding at week 13 was not significantly different between the treatment groups. All three treatments reduced uterine volume, although this decrease was significantly greater in the leuprolide group (47% reduction) than in the ulipristal groups (20-22%). 40% of the leuprolide group reported moderate-to-severe hot flashes, but only 11% (15 mg) and 10% (10 mg) of the ulipristal groups did.

Conclusions: Oral ulipristal acetate (5 mg or 10 mg) is noninferior to intramuscular leuprolide acetate for control of uterine bleeding due to fibroids, and it had a better side-effect profile.

Counselling the Adolescent about Contraception

More than 90% of adolescent pregnancies are unintended, and —50% of all pregnancies occur within the first 6 mo of initiating sexual activity; in addition, 85% of sexually active women become pregnant within 1 yr if no contraception is used and even some of the least effective contraceptive methods markedly decrease the risk of pregnancy.
### Table 7. Classification of Contraceptive Methods (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Effectiveness (perfect use, typical use)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hormonal</strong></td>
<td></td>
</tr>
<tr>
<td>OCP</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Nuva Ring®</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Transdermal (Ortho Evra®)</td>
<td>99.7%, 92%</td>
</tr>
<tr>
<td>Depo-Provera®</td>
<td>99.7%, 97%</td>
</tr>
<tr>
<td>Progestin-only pill (Micronor®)</td>
<td>90-99%</td>
</tr>
<tr>
<td>Mirena® IUS</td>
<td>99.9%</td>
</tr>
<tr>
<td>Jaydess® IUS</td>
<td>99.9%</td>
</tr>
<tr>
<td><strong>Copper IUD</strong></td>
<td>99.3%</td>
</tr>
<tr>
<td><strong>Surgical</strong></td>
<td></td>
</tr>
<tr>
<td>Tubal ligation</td>
<td>99.65%</td>
</tr>
<tr>
<td>Vasectomy</td>
<td>99.9%</td>
</tr>
<tr>
<td><strong>Emergency Postcoital Contraception (EPC)</strong></td>
<td></td>
</tr>
<tr>
<td>Yuzpe® method</td>
<td>98% (within 24 h), decreases by 30% at 72 h</td>
</tr>
<tr>
<td>“Plan B” levonorgestrel only</td>
<td>98% (within 24 h), decreases by 70% at 72 h</td>
</tr>
<tr>
<td>Postcoital IUD</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

Effectiveness: percentage of women reporting no pregnancy after 1 yr of use

## Hormonal Methods

### Combined Oral Contraceptive Pills
- most contain low dose ethinyl estradiol (20-35 μg) plus progestin (norethinedrone, norgestrel, levonorgestrel, desogestrel, norgestimate, drospirenone)
- failure rate (0.3% to 8%) depending on compliance
- monophasic or triphasic formulations (varying amount of progestin throughout cycle)

### Transdermal (Ortho Evra®)
- continuous release of 6 mg norelgestromin and 0.60 mg ethinyl estradiol into bloodstream
- applied to lower abdomen, back, upper arm, buttocks, NOT breast
- worn for 3 consecutive weeks (changed every wk) with 1 wk off to allow for menstruation
- as effective as OCP in preventing pregnancy (>99% with perfect use)
- may be less effective in women >90 kg
- may not be covered by drug plans

### Contraceptive Ring (Nuva Ring®)
- thin flexible plastic ring; releases etonogestrel 120 µg/d and estradiol 15 µg/d
- works for 3 wk then removed for 1 wk to allow for menstruation
- as effective as OCP in preventing pregnancy (98%)
- avoids first pass effect
- side effects: vaginal infections/irritation, vaginal discharge
- may have better cycle control; i.e. decreased breakthrough bleeding

### Starting Hormonal Contraceptives
- thorough history and physical examination, including blood pressure and breast exam
- can start at any time during cycle but ideal if within 5 d of LMP
- follow-up visit 6 wk after hormonal contraceptives prescribed
- pelvic exam not required as STI screening can be done by urine and pap smear screening does not start until >21 yr
### Table 8. Combined Estrogen and Progestin Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Advantages</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ovulatory suppression through inhibition of LH and FSH</td>
<td>• Highly effective</td>
<td>• Estrogen-related: Nausea, Breast changes (tenderness, enlargement), Fluid retention/bloating/edema, Weight gain (rare)</td>
<td>• Absolute: Known/suspected pregnancy, Undiagnosed abnormal vaginal bleeding, Prior thromboembolic events, thromboembolic disorders (Factor V Leiden mutation; protein C or S, or antithrombin III deficiency), active thrombophlebitis, Cerebrovascular or coronary artery disease, Estrogen-dependent tumours (breast, uterus), Impaired liver function associated with acute liver disease, Congenital hypertenyglycemia, Smoker age &gt; 35 yr, Migraines with focal neurological symptoms (excluding aura), Uncontrolled HTN</td>
</tr>
<tr>
<td>• Decidualization of endometrium</td>
<td>• Reversible</td>
<td>• Migraine, headaches</td>
<td>Relative: Migraines (non-focal with aura &lt; 1 h), DM complicated by vascular disease, SLE, Controlled HTN, Hyperlipidemia, Sickle cell anemia, Gallbladder disease</td>
</tr>
<tr>
<td>• Thickening of cervical mucus resulting in decreased sperm penetration</td>
<td>• Cycle regulation, Decreased dysmenorrhea and menorrhagia (less anemia), Decreased benign breast disease and ovarian cyst development, Decreased risk of ovarian and endometrial cancer, Increased cervical mucus which may lower risk of STIs, Decreased PMS symptoms, Improved acne, Osteoporosis protection (possibly)</td>
<td>• Progestin-related: Amenorrhea/breakthrough bleeding, Headaches, Breast tenderness, Increased appetite, Decreased libido, Mood changes, HTN, Acne/oily skin*, Hirsutism*</td>
<td>Drug Interactions/Risks: Rifampin, phenobarbital, phenytoin, griseofulvin, primidone, and St. John’s wort can decrease efficacy, requiring use of back-up method</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• No evidence that OCP is harmful to nursing infant but may decrease milk production; not recommended until 6 wk postpartum, ideally until 3 mo postpartum</td>
</tr>
</tbody>
</table>

Reference: World Health Organization Guidelines for Oral Contraceptive Pill Use

### Table 9. Selected Examples of OCPs

<table>
<thead>
<tr>
<th>Type</th>
<th>Active Compounds (estril and progestin derivative)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alesse®</td>
<td>• 20 µg ethinyl estradiol and 0.5 mg levonorgestrel</td>
<td>• Low dose (20 µg) OCP, Can improve acne and help regulate menstrual cycles</td>
<td>• Low-dose pills can often result in breakthrough bleeding, If this persists for longer than 3 mo, patient should be switched to an OCP with higher estrogen content</td>
</tr>
<tr>
<td>Tri-cyclen®</td>
<td>• 35 µg ethinyl estradiol and 0.180/0.215/0.250 mg norgestimate</td>
<td>• Low androgenic activity can help with acne</td>
<td>• Triphasic OCPs should not be used continuously (unlike monophasic formulations), although should be used continuously for 1 pack</td>
</tr>
<tr>
<td>Yasmin® and Yaz®</td>
<td>• Yasmin®: 30 µg ethinyl estradiol + 3 mg drospirenone (a new progestin), Yaz®: 20 µg ethinyl estradiol + 3 mg drospirenone – 24/4-d pill (4-d pill free interval), Drospirenone has antimineralocorticoid activity and antiandrogenic effects</td>
<td>• Decreased perception of cyclic weight gain/bloating, Fewer PMS symptoms, Improved acne</td>
<td>• Hyperkalemia (rare, contraindicated in renal and adrenal insufficiency), Check potassium if patient also on ACEI, ARB, K⁺-sparing diuretic, heparin, Continue use of spironolactone</td>
</tr>
</tbody>
</table>

#### PROGESTIN-ONLY METHOD

### Table 10. Progestin-ONLY Contraceptive Methods

<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Suitable for postpartum women (does not affect breast milk supply)</td>
<td>• Progestin prevents LH surge, Thickening of cervical mucus, Decrease tubal motility, Endometrial decidualization, Ovulation suppression – oral progestins (not IM) do not consistently suppress compared to combined OCPs</td>
<td>• Irregular menstrual bleeding, Weight gain, Headache, Breast tenderness, Mood changes, Functional ovarian cysts, Acne/oily skin, Hirsutism</td>
<td>Absolute: None</td>
</tr>
<tr>
<td>• Women with contraindications to combined OCP (e.g. thromboembolic or myocardial disease)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Women intolerant of estrogenic side effects of combined OCPs</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Missed Combined OCPs

Miss a ≥1 pill in a row in first wk
• Take 1 pill ASAP, and then the next pill at the usual time
• Use back-up contraception for 7 d; EPC may be necessary

Miss a <3 pills in 2nd or 3rd wk of cycle
• Take 1 pill ASAP, and then continue taking one pill daily until the end of the pack
• Do not take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
• Start the next pack immediately after finishing the previous one
• No need for back-up contraception

Miss ≥3 pills during the 2nd or 3rd wk
• Take 1 pill ASAP, and then continue taking one pill daily until the end of the pack
• Don’t take placebo (28-d packs) or do not take a hormone free interval (21-d packs)
• Start the next pack immediately after finishing the previous one
• Use back-up contraception for 7 d; EPC may be necessary

Irregular breakthrough bleeding often occurs in the first few months after starting OCP; usually resolves after three cycles

Selected Examples of Progestin-Only Methods

Progestin-Only Pill ("minipill")
- Micronor® 0.35 mg norethindrone
- taken daily at same time of day to ensure reliable effect; no pill free interval
- higher failure rate (1.1-13% with typical use, 0.51% with perfect use) than other hormonal methods
- ovulation inhibited in 60% of women; most have regular cycles (but may cause oligo/a menorrhea)
- highly effective if also post-partum breastfeeding, or if >35 yr

Depo-Provera®
- injectable depot medroxyprogesterone acetate
- dose 150 mg IM q12-14wk (convenient dosing)
- initiate within 5 d of beginning of normal menses, immediately postpartum in breastfeeding non-breastfeeding women
- irregular spotting progresses to complete amenorrhea in 70% of women (after 1-2 yr of use)
- highly effective 99%; failure rate 0.3%
- side effect: decreased bone density (may be reversible)
- disadvantage: restoration of fertility may take up to 1-2 yr

Table 11. IUS/IUD Contraceptive Methods

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copper-Containing IUD</td>
<td>• Both Copper and Progesterone IUD</td>
<td>Absolute</td>
</tr>
<tr>
<td>(Nova-T®)</td>
<td>• Breakthrough bleeding</td>
<td>• Both Copper and Progesterone IUD</td>
</tr>
<tr>
<td></td>
<td>• Expulsion (5% in the 1st yr, greatest in 1st mo and in nulliparous women)</td>
<td>• Known or suspected pregnancy</td>
</tr>
<tr>
<td></td>
<td>• Uterine wall perforation (1/1,000) on insertion</td>
<td>• Undiagnosed genital tract bleeding</td>
</tr>
<tr>
<td></td>
<td>• If pregnancy occurs with an IUD, increased risk of ectopic</td>
<td>• Acute or chronic PID</td>
</tr>
<tr>
<td></td>
<td>• Increased risk of PID (within first 10 d of insertion only)</td>
<td>• Lifestyle risk for STIs*</td>
</tr>
<tr>
<td></td>
<td>• Copper IUD: increased blood loss and duration of menses, dysmenorrhea</td>
<td>Copper IUD</td>
</tr>
<tr>
<td></td>
<td>• Progestrone IUD: bloating, headache</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td></td>
<td>• Both Copper and Progesterone IUD</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>• Valvular heart disease</td>
<td>• Both Copper and Progesterone IUD</td>
</tr>
<tr>
<td></td>
<td>• Past history of PID or ectopic pregnancy</td>
<td>• Known allergy to copper</td>
</tr>
<tr>
<td></td>
<td>• Presence of prostheses</td>
<td>• Wilson’s disease</td>
</tr>
<tr>
<td></td>
<td>• Abnormalities of uterine cavity, intracavitary fibroids</td>
<td>Relative</td>
</tr>
<tr>
<td></td>
<td>• Cervical stenosis</td>
<td>• Copper IUD: severe dysmenorrhea or amenorrhea</td>
</tr>
<tr>
<td></td>
<td>• Immunosuppressed individuals (e.g. HIV)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Copper IUD: severe dysmenorrhea or amenorrhea</td>
<td></td>
</tr>
</tbody>
</table>

*Cervical swabs for gonorrhea and chlamydia should be done prior to insertion

Intrauterine Device

Steroidal Contraceptives and Bone Fractures in Women: Evidence from Observational Studies
Cochrane DB Syst Rev 2012;3:CD008480

Purpose: To review evidence from observational studies of hormonal contraceptive use and the risk of bone fracture.

Selection Criteria: Cohort and case-control studies of hormonal contraceptive use with fracture risk as the primary outcome.

Results: 7 case-control and 7 cohort studies. Overall, little evidence for an association between OCP use and fracture risk. One study reported increased fracture risk for ever-use of DMPA (OR 1.14, 95% CI 1.01-1.26) and the second also noted increased risk for any past use of DMPA (OR 1.13, 95% CI 1.07-1.21). One study reported reduced risk for ever-use of hormonal IUD (OR 0.75, 95% CI 0.64-0.87).

Conclusion: Observational studies do not indicate an overall association between OCP use and fracture risk. DMPA users may have an increased fracture risk.

Continuous or Extended Cycle vs. Cyclic Use of Combined Oral Contraceptives for Contraception

Background: The efficacy and side effects of cyclic administration or extended use (longer periods of active pills and/or shorter periods placebo) or continuous use (uninterrupted active pill administration) of combination oral contraceptives (COC) are unclear.

Study: Systematic review of randomized clinical trials comparing continuous or extended vs. cyclic COC administration.

Findings: Eight RCTs met inclusion criteria.
- No difference in efficacy of pregnancy prevention.
- No difference in compliance with dosing schedules.
- Extended cycle use lowered prevalence of menstrual symptoms (e.g. headaches, pain, fatigue).
- No difference in bleeding patterns, but continuous use may improve over time.

Depot Medroxyprogesterone Acetate and Bone Effects
ACOG Committee Opinion 415, 2008
Obstet Gynecol 2008;112:127-30
- The effect of DMPA on BMD should neither prevent practitioners from prescribing DMPA nor limit its use to 2 consecutive yr.
- The greatest loss of BMD occurs in the first 1-2 yr of DMPA use.
- Contraceptive implants and intrauterine devices that do not affect BMD should be considered as first-line for adolescents.
- Inform patients about benefits and the potential risks of DMPA, and encourage daily exercise, calcium and vitamin D intake.
- Routine BMD monitoring is not recommended for DMPA users.
## Emergency Postcoital Contraception

### Table 12. Emergency Contraceptive Methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Mechanism of Action</th>
<th>Side Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HORMONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Yuzpe Method</strong></td>
<td>Used within 72 h of unprotected intercourse; limited evidence of benefit up to 5 d</td>
<td>• Unknown; theories include:</td>
<td>• Pre-existing pregnancy (although not teratogenic)</td>
</tr>
<tr>
<td></td>
<td>• Ovral® 2 tablets then repeat in 12 h (ethinyl estradiol 100 µg/levonorgestrel 500 µg)</td>
<td>• Suppresses ovulation or causes deficient luteal phase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can substitute with any OCP as long as same dose of estrogen used</td>
<td>• Averts endometrium to prevent implantation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 2% overall risk of pregnancy</td>
<td>• Affects sperm/ova transport</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Efficacy decreased with time (e.g. less effective at 72 h than 24 h)</td>
<td>• Nausea (due to estrogen; treat with Gravol®)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Irregular spotting</td>
<td></td>
</tr>
<tr>
<td>“Plan B”</td>
<td>Consists of levonorgestrel 750 µg q12h for 2 doses (can also take 2 doses together); taken within 72 h of intercourse</td>
<td>• Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td>• Greater efficacy (75-95% if used within 24 h) and better side effect profile than Yuzpe method but efficacy decreases with time; 1st line if &gt;24 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• No estrogen thus very few contraindications/side effects (less nausea)</td>
<td>• Headache, hot flashes, constipation, vertigo, endometrial thickening</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Less effective in overweight individuals (&gt;75 kg less effective, &gt;80 kg not recommended)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulipristal</td>
<td>30 mg PO within 5 d</td>
<td>• Selective Progesterone Receptor Modulator (SPERM) with primarily antiprogestin activity:</td>
<td>Same as above</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• may delay ovulation by up to 5 d</td>
<td></td>
</tr>
<tr>
<td><strong>NON-HORMONAL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Postcoital IUD (Copper)</td>
<td>Insert up to 7 d postcoitus</td>
<td>• See Table 11</td>
<td>See Table 11</td>
</tr>
<tr>
<td></td>
<td>• Prevents implantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 1% failure rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Can use for short duration in higher risk individuals</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Mirena® IUS cannot be used as EPC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Follow-up

- 3–4 wk post treatment to confirm efficacy (confirmed by spontaneous menses or pregnancy test)
- contraception counseling

## Termination of Pregnancy

### Definition
- active termination of a pregnancy before fetal viability (usually <500 g or <20 wk GA)

### Indications
- inability to carry a pregnancy to term due to medical or social reasons (including patient preference)

### Management
- **medical**
  - <9 wk: methotrexate + misoprostol
  - >12 wk: prostaglandins (intra- or extra-amniotically or IM) or misoprostol
- **surgical**
  - <12 wk: dilatation + vacuum aspiration ± curettage
  - >12 wk: dilatation and evacuation, early induction of labour
- common complications: pain or discomfort
- less common complications: hemorrhage, perforation of uterus, laceration of cervix, risk of infertility, infection/endometritis, Asherman's syndrome (adhesions within the endometrial cavity causing amenorrhea/infertility), retained products of conception
- counselling
  - supportive and counselling services
  - future contraception and family planning services
  - ensure follow-up

Any OCP can be used as EPC; 100 µg ethinyl estradiol PO q12h x 2 doses
- Levonorgestrel emergency contraception regimens are more effective and cause fewer side effects than the Yuzpe regimen
- Levonorgestrel emergency contraception single dose (1.5 mg) and the 2-dose levonorgestrel regimen (0.75 mg 12 h apart) have similar efficacy with no difference in side effects


CMA Policy (1988)
“Induced abortion should be uniformly available to all women in Canada” and "there should be no delay in the provision of abortion services"

Terminations are generally done until the stage of viability (~23.5 wk), although this varies depending on the provider
Pregnancy-Related Complications

Spontaneous Abortions

• see Termination of Pregnancy, for therapeutic abortions

Table 13. Classification of Spontaneous Abortions

<table>
<thead>
<tr>
<th>Type</th>
<th>History</th>
<th>Clinical</th>
<th>Management (± Rhogam®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Threatened</td>
<td>Vaginal bleeding ± cramping</td>
<td>Cervix closed and soft</td>
<td>Watch and wait &lt;5% go on to abort</td>
</tr>
</tbody>
</table>
| Inevitable   | Increasing bleeding and cramps ± rupture of membranes | Cervix closed until products start to expel, then external os opens | a) Watch and wait  
               |                                |                                  | b) Misoprostol 400-800 µg PQ/PV  
               |                                |                                  | c) D&C ± oxytocin               |
| Incomplete   | Extremely heavy bleeding and cramps ± passage of tissue noticed | Cervix open                       | a) Watch and wait  
               |                                |                                  | b) Misoprostol 400-800 µg PQ/PV  
               |                                |                                  | c) D&C ± oxytocin               |
| Complete     | Bleeding and complete passage of sac and placenta | Cervix closed, bleeding stopped   | No D&C — expectant management         |
| Missed       | No bleeding (fetal death in utero) | Cervix closed                     | a) Watch and wait  
               |                                |                                  | b) Misoprostol 400-800 µg PQ/PV  
               |                                |                                  | c) D&C ± oxytocin               |
| Recurrent    | ≥3 consecutive spontaneous abortions |                                | Evaluate mechanical, genetic,  
               |                                |                                  | environmental, and other risk factors |
| Septic       | Contents of uterus infected — infrequent |                                | D&C                                  |

Ectopic Pregnancy

Definition

• embryo implants outside of the endometrial cavity

Figure 13. Sites of ectopic pregnancy implantation

Amphullary (70%) >> isthmal (12%) > fimbrial (11%) > ovarian (3%) > interstitial (2%) > abdominal (1%)

Epidemiology

• 1/100 pregnancies
• fourth leading cause of maternal mortality, leading cause of death in first trimester
• increase in incidence over the last 3 decades
• three commonest locations for ectopic pregnancy: ampullary (70%), isthmic (12%), fimbrial (11%)
Etiology
- 50% due to damage of fallopian tube cilia following PID
- intrinsic abnormality of the fertilized ovum
- conception late in cycle
- transmigration of fertilized ovum to contralateral tube

Risk Factors
- previous ectopic pregnancy
- gynecologic
  - current IUD use – increased risk of ectopic if pregnancy occurs
  - history of PID (especially infection with C. trachomatis), salpingitis
  - infertility
  - infertility treatment (IVF pregnancies following ovulation induction [7% ectopic rate])
- previous procedures
  - any surgery on fallopian tube (for previous ectopic, tubal ligation, etc.)
  - abdominal surgery for ruptured appendix, etc.
- smoking
- structural
  - uterine leiomyomas
  - adhesions
  - abnormal uterine anatomy (e.g. T-shaped uterus)

Investigations
- serial β-hCG levels; normal doubling time with intrauterine pregnancy is 1.6-2.4 d in early pregnancy
- rise of <20% of β-hCG is 100% predictive of a non-viable pregnancy
- prolonged doubling time, plateau, or decreasing levels before 8 wk implies nonviable gestation but does not provide information on location of implantation
- 85% of ectopic pregnancies demonstrate abnormal β-hCG doubling
- ultrasound
  - U/S is only definitive if fetal cardiac activity is detected in the tube or uterus
  - specific finding on transvaginal U/S is a tubal ring
- laparoscopy (sometimes used for definitive diagnosis)

Treatment
- goals of treatment: conservative (preserve tube if possible), maintain hemodynamic stability
- surgical = laparoscopy
  - linear salpingostomy an option if tube salvageable
  - salpingectomy if tube damaged or ectopic is ipsilateral recurrence
- 15% risk of persistent trophoblast; must monitor β-hCG titres weekly until they reach non-detectable levels
- consider Rhogam® if Rh negative
- may require laparotomy if patient is unstable, extensive abdominal surgical history, etc.
- medical = methotrexate (for indications see Figure 4)
  - use 50 mg/m² body surface area; given in a single IM dose
  - this is 1/5 to 1/6 chemotherapy dose, therefore minimal side effects (reversible hepatic dysfunction, diarrhea, gastritis, dermatitis)

DDX of Lower Abdominal Pain
• Urinary tract: UTI, kidney stones
• GI: diverticulitis, appendicitis
• Gyn: endometriosis, PID, fibroid (degenerating, infarcted, torsion), ovarian torsion, ovarian neoplasm, ovarian cyst, pregnancy-related

Clinical Features of Ectopic Pregnancy
4Ts and 1S
- Temperature >38°C (20%)
- Tenderness: abdominal (80%) ± rebound (45%)
- Tenderness on bimanual examination, cervical motion tenderness
- Tissue: palpable adnexal mass (50%) (half have contralateral mass due to lutein cyst)
- Signs of pregnancy (e.g. Chadwick’s sign, Hegar’s sign)

Management of Abortions
• Always rule out an ectopic
• Always check Rh; if negative, give Rhogam®
• Always ensure patient is hemodynamically stable
follow β-hCG levels weekly until β-hCG is non-detectable
- plateau or rising levels suggest persisting trophoblastic tissue (requires further treatment)
- 82-95% success rate, but up to 25% will require a second dose
- tubal patency following methotrexate treatment approaches 80%

Prognosis
- 9% of maternal deaths during pregnancy
- 40-60% of patients will become pregnant again after surgery
- 10-20% will have subsequent ectopic pregnancy

Infertility

Epidemiology
- 10-15% of couples
- must investigate both members of the couple

Female Factors

Etiology
- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
  - stress, poor nutrition, excessive exercise (even with presence of menstruation)
  - PCOS
  - ovarian
  - premature ovarian failure
  - luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, Cushing’s syndrome, renal/hepatic failure)
  - congenital (Turner’s syndrome, gonadal dysgenesis or gonadotropin deficiency)
- tubal factors (20-30%)
  - PID
  - adhesions (previous surgery, peritonitis, endometriosis)
  - ligation/occlusion (e.g. previous ectopic pregnancy)
- uterine factors (<5%)
  - congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure
  - intrauterine adhesions (e.g. Asherman’s syndrome)
  - infection (endometritis, pelvic TB)
  - fibroids/polyps (particularly intrauterine)
  - endometrial ablation
  - cervical factors (5%)
  - hostile or acidic cervical mucus
  - anti-sperm antibodies
  - structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

Investigations
- ovulatory
  - day 3: FSH, LH, TSH, prolactin ± DHEA, free testosterone (if hirsute) add estradiol for proper FSH interpretation
  - day 21-23: serum progesterone to confirm ovulation
  - initiate basal body temperature monitoring (biphasic pattern)
  - postcoital test: evaluate mucus for clarity, pH, spinnbarkeit/fibrosity (rarely done)
- tubal factors
  - HSG (can be therapeutic – opens fallopian tube)
  - SHG (can be therapeutic; likely less – opens fallopian tube)
  - laparoscopy with dye insufflation (or tubal dye test)
- peritoneal/uterine factors
  - HSG/SHG, hysteroscopy
  - other
  - karyotype

requirements for Conception
- Ovary
- Tube
- Cervix
- Endometrium
- Sperm

When Should Investigations Begin?
- < 35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after > 6 mo
- > 40 yr: immediately
- Earlier if
  - history of PID
  - history of infertility in previous relationship
  - prior pelvic surgery
  - chemotherapy/radiation in either partner
  - recurrent pregnancy loss
  - moderate-severe endometriosis

Controversial and Evolving Ethical Issues
- Infertility demands non-judgmental discussion
- Ethical issues surrounding therapeutic donor insemination in same sex couples, surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
- If the doctor finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician
Treatment
• education: timing of intercourse in relation to ovulation (from 2 d prior to 2 d following presumed ovulation), every other day
• medical
  • ovulation induction
    • clomiphene citrate (Clomid®): estrogen antagonist that causes a perceived decreased estrogen state, resulting in increased pituitary gonadotropins; causes increased FSH and LH, leading to ovulation induction (works much better if anovulatory)
    • followed by β-hCG for stimulation of ovum release
  • may add
    • bromocriptine (dopamine agonist) if elevated prolactin
    • dexamethasone for hyperandrogenism (adult onset congenital adrenal hyperplasia)
    • metformin (for PCOS)
  • luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
  • ASA (81 mg PO OD) for women with a history of recurrent spontaneous abortions
• surgical/procedural
  • tubuloplasty
  • lysis of adhesions
  • artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  • sperm washing
  • IVF (in vitro fertilization)
  • IFT (intrafallopian transfer)
  • GIFT* (gamete intrafallopian transfer): immediate transfer with sperm after oocyte retrieval
  • ZIFT* (zygote intrafallopian transfer): transfer after 24 h culture of oocyte and sperm
  • TET* (tubal embryo transfer): transfer after >24 h culture
  • ICSI (intracytoplasmic sperm injection)
  • IVM (in vitro maturation)
  • ± oocyte or sperm donors
  • ± pre-genetic screening for single gene defects in karyotype of zygote
  • *Not performed in Canada

Male Factors
• see Urology, U34

Etiology
• varicocele (>40%)
• idiopathic (>20%)
• obstruction (~15%)
• cryptorchidism (~8%)
• immunologic (~3%)

Investigations
• semen analysis and culture
• postcoital (Huhner) test: rarely done

Polycystic Ovarian Syndrome
• also called chronic ovarian androgenism

Etiology

Figure 15. Pathophysiology of polycystic ovarian syndrome
Diagnosis

- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence - hirsutism or male pattern alopecia or
    - biochemical evidence - raised free testosterone
  - polycystic ovaries on U/S

Clinical Features

- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- insulin resistance occurs in both lean and obese patients
- anacneosis nigricans: browning of skin folds in intertriginous zones (indicative of insulin resistance)
- family history of DM

Investigations

- goal of investigations is to identify hyperandrogenism or chronic anovulation; and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, 17-hydroxyprogesterone, free testosterone, DHEA-S, TSH, free T₄, androstenedione, SHBG
  - LH:FSH >2:1; LH is chronically high with FSH mid-range or low (low sensitivity and specificity)
  - increased DHEA-S, androstenedione and free testosterone (most sensitive), decreased SHBG
  - transvaginal or transabdominal U/S: polycystic-appearing ovaries ("string of pearls" – 12 or more small follicles 2-9 mm, or increased ovarian volume)
  - tests for insulin resistance or glucose tolerance
    - fasting glucose:insulin ratio <4.5 is consistent with insulin resistance (U.S. units)
    - 75 g OGTT yearly (particularly if obese)
  - laparoscopy
    - not required for diagnosis
    - most common to see white, smooth, sclerotic ovaries with a thick capsule; multiple follicular cysts in various stages of atresia; hyperplastic theca and stroma
    - rule out other causes of abnormal bleeding

Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - OCP monthly or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if type 2 diabetic or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- infertility
  - medical induction of ovulation: clomiphene citrate, human menopausal gonadotropins (HMG [Pergonal®]), LHRH, recombinant FSH, and metformin
  - metformin may be used alone or in conjection with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary
  - bromocriptine (if hyperprolactinemia)
- hirsutism
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drosperone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
    - finasteride (5-a reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone: androgen receptor inhibitor

Gynecological Infections

Physiologic Discharge

- clear, white, flocculent, odorless discharge; pH 3.8-4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

PCOS may be Confused with

- Late onset congenital adrenal hyperplasia (21-hydroxylase deficiency)
- Cushing’s syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism

Clinical Signs of Endocrine Imbalance

- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Infertility
- Obesity
- Sleep apnea

Long-Term Health Consequences

- Hyperandrogenemia
- Adult-onset DM
- Hypertension
- NIDDM
- Hypothyroidism
- Hyperlipidemia
- Raynaud's phenomenon
- Hypercoagulability
- Impaired glucose tolerance

Use of Metformin in Polycystic Ovary Syndrome: A Meta-Analysis


Study: This meta-analysis of 17 RCTs assessed the efficacy of metformin or metformin in combination with clomiphene citrate in women with PCOS who were seeking pregnancy.

Main Outcomes: Ovulation, pregnancy, and live birth. Patients: 1,639 patients with PCOS were followed up for up to 12 mo.

Results: Compared to placebo, metformin increased the odds of ovulation (OR 2.94, 95% CI 1.43-6.02). However, when used alone, metformin did not significantly increase the odds of achieving pregnancy (OR 1.56, 95% CI 0.74-3.33). When compared to clomiphene alone, the combination of metformin and clomiphene increased the likelihood of ovulation (OR 4.39, 95% CI 1.94-9.96) and pregnancy (OR 2.67, 95% CI 1.45-4.94). The effect of combination therapy was most prominent in clomiphene-resistant and obese women with PCOS. Furthermore, the combination therapy had a higher likelihood of having a live birth compared to clomiphene alone, but this did not reach significance (OR 1.74, 95% CI 0.79-3.86).

Conclusion: Metformin increases the likelihood of ovulation. When used together with clomiphene, metformin increases the likelihood of both ovulation and pregnancy, especially in clomiphene-resistant and obese women.

Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies

JOGC 2008;111(4):959-68

At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on basis of menstrual cycle history of poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multi-factorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.
Vulvovaginitis

PREPUBERTAL VULVOVAGINITIS

- clinical features
  - irritation, pruritus
  - discharge
  - vulvar erythema
  - vaginal bleeding (specifically due to Group A Streptococci and Shigella)

- differential diagnosis
  - non-specific vulvovaginitis (25-75%)
  - infections (respiratory, enteric, systemic, sexually acquired)
  - foreign body (toilet paper most common)
  - Candida (if using diapers)
  - pinworms
  - polyps, tumour (ovarian malignancy)
  - vulvar skin disease (lichen sclerosis, condyloma acuminata)
  - trauma (accidental straddle injury, sexual abuse)
  - psychosomatic vaginal complaints (specific to vaginal discharge)
  - endocrine abnormalities (specific to vaginal bleeding)
  - blood dyscrasia (specific to vaginal bleeding)

- etiology
  - infectious
    - poor hygiene, proximity of vagina to anus
    - recent infection (respiratory, enteric, systemic)
    - STI: investigate sexual abuse
  - non-specific
    - lack of protective hair and labial fat pads
    - lack of estrogenization
    - susceptible to chemicals, soaps (bubble baths), medications, and clothing
    - enuresis

- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen), pH, wet-mount, and KOH smear in adults only

- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - A&D® dermatological ointment (vitamin A/D) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified

Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Treatment</th>
<th>Tissue</th>
<th>Examination</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cellophane tape test</td>
<td>Empirical treatment with mebendazole</td>
<td>Area of white patches and thinning of skin</td>
<td>Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia</td>
<td></td>
</tr>
</tbody>
</table>

POSTMENOPAUSAL VAGINITIS/ATROPHIC VAGINITIS

- clinical features
  - dyspareunia
  - postcoital spotting
  - mild pruritus

- investigations
  - atrophy is usually a visual diagnosis: thinning of tissues, erythema, petechiae, bleeding points, dryness on speculum exam
  - rule out malignancy: especially endometrial cancer

- treatment
  - local estrogen replacement (ideal): Premarin® cream, VagiFem® tablets, or Estring®
  - oral or transdermal hormone replacement therapy (if treatment for systemic symptoms is desired)
  - good hygiene
Table 15. Infectious Vulvovaginitis

<table>
<thead>
<tr>
<th>Organisms</th>
<th>Bacterial Vaginosis (BV)</th>
<th>Trichomoniasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candida albicans (90%)</td>
<td>Gardnerella vaginalis</td>
<td>Trichomonas vaginalis (flagellated protozoan)</td>
</tr>
<tr>
<td>Candida glabrata (&lt;5%)</td>
<td>Mycoplasma hominis</td>
<td></td>
</tr>
<tr>
<td>Candida tropicalis (&lt;5%)</td>
<td>Anaerobes: Prevotella, Mobiluncus, Bacteroides</td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology or Transmission
- Predisposing factors include:
  - Immunosuppressed host (DM, AIDS, etc.)
  - Recent antibiotic use
  - Increased estrogen levels (e.g., pregnancy, OCP)
- Replacement of vaginal Lactobacillus with organisms above
- Sexual transmission

Discharge
- White, "cottage cheese," minimal
- Grey, thin, diffuse
- Yellow-green, malodorous, diffuse, frothy

Other
- 20% asymptomatic
- Fishy odor, especially after coitus
- Occasional irritated tender vulva

Signs/Symptoms
- Intense pruritus
- Swollen, inflamed genitals
- Vulvar burning, dysuria, dyspareunia
- Absence of vulvar/vaginal irritation
- Petechiae on vagina and cervix

pH
- ≤ 4.5
- ≥ 4.5

Saline Wetmount
- KOH wetmount reveals hyphae and spores
- >20% clue cells = squamous epithelial cells dotted with coccobacilli (Gardnerella)
- Paucity of WBC
- Paucity of Lactobacilli
- Positive whiff test: fishy odor with addition of KOH to slide (due to formation of amines)

Treatment
- Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments
- No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure
- Oral
  - Metronidazole 500 mg PO bid x 7 d
  - Clindamycin 2% 5 g intravaginally at bedtime for 7 d
  - Probiotics (lactobacillus sp.): oral or topical alone or as adjuvant

Other
- Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole
- Routine treatment of partner(s) not recommended (not sexually transmitted)
- Associated with recurrent preterm labour, preterm birth, and postpartum endometritis
- Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)
- Routine treatment of partner(s) not recommended (not sexually transmitted)
- Warnings accompanying metronidazole use
- Treat partner(s)

Sexually Transmitted Infections
- see Family Medicine, FM45

CDC Notifiable Diseases
- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis

Risk Factors for STIs
- History of previous STI
- Contact with infected person
- Sexually active individual < 25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Street involvement (homelessness, drug use)
TRICHOMONIASIS
• see Infectious Vulvovaginitis, Table 15, GY27

CHLAMYDIA

Etiology
• Chlamydia trachomatis

Epidemiology
• most common bacterial STI in Canada
• often associated with N. gonorrhoeae

Clinical Features
• asymptomatic (80% of women)
• muco-purulent endocervical discharge
• urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
• pelvic pain
• postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
• symptomatic sexual partner

Investigations
• cervical culture or nucleic acid amplification test
• obligate intracellular parasite: tissue culture is the definitive standard
• urine and vaginal tests now available, which are equally or more effective than cervical culture

Treatment
• doxycycline 100 mg PO bid for 7 d or azithromycin 1 g PO in a single dose (may use in pregnancy)
• also treat gonorrhea because of high rate of co-infection
• treat partners
• reportable disease
• test of cure for chlamydia required in pregnancy (cure rates lower in pregnant patients) → retest 3-4 wk after initiation of therapy

Screening
• high risk groups
• during pregnancy
• with initiation of OCP (independent risk factor)

Complications
• acute salpingitis, PID
• Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
• reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
• infertility: tubal obstruction from low grade salpingitis
• ectopic pregnancy
• chronic pelvic pain
• perinatal infection: conjunctivitis, pneumonia

GONORRHEA

Etiology
• Neisseria gonorrhoeae
• symptoms and risk factors same as with chlamydia

Investigations
• Gram stain shows Gram-negative intracellular diplococci
• cervical, rectal, and throat culture (if clinically indicated)

Treatment
• single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
• if pregnant: above regimen or 2 g spectinomycin IM plus azithromycin 1 g PO (avoid quinolones)
• also treat chlamydia, because of high rate of co-infection
• treat partners
• reportable disease
• screening as with chlamydia

Test of cure for C. trachomatis and N. gonorrhoeae is not routinely indicated
Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant

STI Testing
• Vaginal swab
  • Tests for bacterial vaginosis, trichomoniasis, candida
• Cervical swab
  • Tests for gonorrhea and chlamydia
HUMAN PAPILLOMAVIRUS

Etiology
- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma

Clinical Features
- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

Investigations
- cytology (see Cervical Screening Pap Test, GY44)
- koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

Treatment
- patient administered
  - podofilox 0.5% solution or gel bid x 3 d in a row (4 d off) then repeat x 4 wk
  - imiquimod (Aldara®) 5% cream 3x/wk qhs x 16 wk
- provider administered
  - cryotherapy with liquid nitrogen: repeat q1-2wk
  - podophyllin resin in tincture of benzoin: weekly
  - trichloroacetic acid (TCA) or bichloroacetic acid weekly (80-90%); safe in pregnancy
  - surgical removal/laser
  - intralesional interferon

Prevention
- vaccination: Gardasil®, Cervarix® see Table 25, GY46
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

HERPES SIMPLEX VIRUS OF VULVA

Etiology
- 90% are HSV-2, 10% are HSV-1

Clinical Features
- may be asymptomatic
- initial symptoms: present 2-21 d following contact
- prodromal symptoms: tingling, burning, pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: less severe, less frequent and shorter in duration (especially with HSV-1)

Investigations
- viral culture preferred in patients with ulcer present, however decreased sensitivity as lesions heal
- cytologic smear (Tzanck smear)
  - multinucleated giant cells, acidophilic intranuclear inclusion bodies
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not available routinely in Canada)
- HSV DNA PCR
Treatment

- first episode
  - acyclovir 200 mg PO five times daily x 5-10 d, or famciclovir 250 mg PO tid x 7-10 5 d, or valacyclovir 1 g PO bid x 10 d
- recurrent episode
  - acyclovir 200 mg PO five times daily x 5 d, or famciclovir 125 mg PO bid x 5 d, or valacyclovir 500 mg PO bid OR 1 g PO OD x 3 d
- daily suppressive therapy
  - consider if more than 6 recurrences per yr or one every 2 mo
  - acyclovir 400 mg PO bid, or famciclovir 250 mg bid, or valacyclovir 0.5-1 g PO OD
- severe disease
  - consider IV therapy: acyclovir 55 mg/kg IV over 60 min q8h
- education regarding transmission
  - avoid contact from onset of prodrome until lesions have cleared
  - use barrier contraception

SYphilIS

Etiology
- Treponema pallidum

Classifications

- primary syphilis
  - 3-4 wk after exposure
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection
  - nonspecific symptoms: malaise, anorexia, headache, diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, limbs
  - condylomata lata: anogenital, broad-based fleshy grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only
- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, general paresis
  - cardiovascular: aortic aneurysm, dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

Investigations

- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis)
- spirochetes
- non-treponemal screening tests (VDRL, RPR); nonreactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
- confirmatory tests; remain reactive for life (even after adequate treatment)

Treatment

- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
  - treat partners, reportable disease
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units IM q4h x 10-14 d
- screening
  - high risk groups
  - in pregnancy (see Obstetrics, Table Infections During Pregnancy, OB30)

Complications

- if untreated, 1/3 will experience late complications

HIV

- see Infectious Diseases, ID28
## Bartholinitis/Bartholin Gland Abscess

**Etiology**
- Often anaerobic and polymicrobial
- *U. urealyticum, N. gonorrhoeae, C. trachomatis, E. coli, P. mirabilis, Streptococcus spp., S. aureus* (rare)
- Blockage of duct

**Clinical Features**
- Unilateral swelling and pain in inferior lateral opening of vagina
- Sitting and walking may become difficult and/or painful

**Treatment**
- Sitz baths, warm compresses
- Antibiotics: cephalexin x 1 wk
- Incision and drainage using local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
- Marsupialization under general anesthetic – more definitive treatment
- Rarely treated by removing gland

## Pelvic Inflammatory Disease

- Up to 20% of all gynecology-related hospital admissions

**Etiology**
- Causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
  - Gonorrhea and chlamydia often co-exist
  - Endogenous flora: anaerobic, aerobic, or both
    - *E. coli, Staphylococcus, Streptococcus, Enterococcus, Bacteroides, Peptostreptococcus, H. influenzae, G. vaginalis*
  - Cause of recurrent PID
  - Associated with instrumentation
  - *Actinomyces israelii* (Gram-positive, non acid-fast anaerobe)
  - 1-4% of PID cases associated with IUDs
  - Others (TB, Gram-negatives, CMV, *U. urealyticum*, etc.)

**Risk Factors**
- Age <30 yr
- Risk factors as for chlamydia and gonorrhea
- Vaginal douching
- IUD (within first 10 d after insertion)
- Invasive gynecologic procedures (D&C, endometrial biopsy)

**Clinical Presentation**
- Up to 2/3 asymptomatic: many subtle or mild symptoms
  - Common
    - Fever >38.3°C
    - Lower abdominal pain and tenderness
    - Abnormal discharge: cervical or vaginal
  - Uncommon
    - N/V
    - Dysuria
    - AUB
  - Chronic disease (often due to chlamydia)
    - Constant pelvic pain
    - Dyspareunia
    - Palpable mass
    - Very difficult to treat, may require surgery
Investigations
- blood work
  - β-hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine R&M
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - cervical cultures for *N. gonorrhoeae*, *C. trachomatis*
  - endometrial biopsy will give definitive diagnosis (rarely done)
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy (gold standard)
  - for definitive diagnosis: may miss subtle inflammation of tubes or endometritis

Treatment
- must treat with polymicrobial coverage
- inpatient if
  - moderate to severe illness
  - atypical infection
  - adnexal mass, tubo-ovarian or pelvic abscess
  - unable to tolerate oral antibiotics or failed oral therapy
  - immunocompromised
  - pregnant
  - adolescent – first episode
  - surgical emergency cannot be excluded (e.g. ovarian torsion)
- PID is secondary to instrumentation
- recommended treatment
  - cefoxitin 2 g IV q6h (no longer available in U.S.A.) + doxycycline 100 mg IV/PO q12h or clindamycin 900 mg IV q8h + gentamicin 2 mg/kg IV/IM loading dose then gentamicin 1.5 mg/kg IV q8h maintenance dose
  - continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO bid to complete 14 d
  - percutaneous drainage of abscess under U/S guidance
  - when no response to treatment, laparoscopic drainage
  - if failure, treatment is surgical (salpingectomy, TAH/BSO)
- outpatient if
  - typical findings
  - mild to moderate illness
  - oral antibiotics tolerated
  - compliance ensured
  - follow-up within 48–72 h (to ensure symptoms not worsening)
- recommended treatment
  - ceftriaxone 250 mg IM x 1 + doxycycline 100 mg PO bid x 14 d or cefoxitin 2 g IM x 1 + probenecid 1 g PO + doxycycline 100 mg PO bid ± metronidazole 500 mg PO bid x 14 d
  - ofloxacin 400 mg PO bid x 14 d or levofloxacin 500 mg PO OD x 14 d ± metronidazole 500 mg PO bid x 14 d
  - consider removing IUD after a minimum of 24 h of treatment
  - reportable disease
  - treat partners
  - consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection

Complications of Untreated PID
- chronic pelvic pain
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID → 13% infertility
  - 2 episodes of PID → 36% infertility
- bacteremia
- septic arthritis, endocarditis
**Toxic Shock Syndrome**

- **Risk Factors**
  - tampon use
  - diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
  - wound infections
  - post-partum infections
  - early recognition and treatment of syndrome is imperative as incorrect diagnosis can be fatal

- **Clinical Presentation**
  - sudden high fever
  - sore throat, headache, diarrhea
  - erythroderma
  - signs of multisystem organ failure
  - refractory hypotension
  - exfoliation of palmar and plantar surfaces of the hands and feet 1-2 wk after onset of illness

- **Treatment**
  - remove potential sources of infection (foreign objects and wound debris)
  - debride necrotic tissues
  - adequate hydration
  - penicillinase-resistant antibiotics, e.g. cloxacillin
  - steroid use controversial but if started within 72 h, may reduce severity of symptoms and duration of fever

**Surgical Infections**

- **Post-Operative Infections in Gynecological Surgery**
  - pelvic cellulitis
    - common post hysterectomy, affects vaginal vault
    - erythema, induration, tenderness, discharge involving vaginal cuff
    - treat if fever and leukocytosis with broad spectrum antibiotics, i.e. clindamycin and gentamicin
    - drain if excessive purulence or large mass
    - can result in intra-abdominal and pelvic abscess
  - see General Surgery, Post-Operative Fever, GS7

**Sexual Abuse**

- see Family Medicine, FM27, Emergency Medicine, ER27

**Sexuality and Sexual Dysfunction**

**SEXUAL RESPONSE**

1. desire: energy that allows an individual to initiate or respond to sexual stimulation
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

**SEXUAL DYSFUNCTION**

**Etiology**

- psychological or emotional: depression, abuse
- hormonal: menopause
- neurologic dysfunction: spinal cord injury
- vascular insufficiency: DM
- drug side effects: β-blockers
- trauma: episiotomy
Classification
• lack of desire (60-70% of women)
• lack of arousal
• anorgasmia (5-10%)
  • primary anorgasmia: never before achieved orgasm under any circumstances
  • secondary anorgasmia: was able to achieve orgasms before but now unable to
• dyspareunia (3-6%): painful intercourse, superficial or deep
  • vaginismus (15%)
  • vulvodynia
  • vaginal atrophy
  • vulvar vestibulitis: associated with history of frequent yeast infections
  • PID

Treatment
• lack of desire: assess factors, rule out organic causes, relationship therapy, sensate focus exercises
• anorgasmia: self-exploration/pleasuring, relationship therapy if needed, bridging techniques (different sexual positions, clitoral stimulation during intercourse)
• dyspareunia
  • Kegel and reverse Kegel exercises
  • dilator treatment
  • comfort with self-exam
  • psychotherapy, other behavioural techniques
  • female on top position: allows for control of speed and duration
  • vestibulitis: remove local irritants, change in contraceptive methods, dietary changes (increased citrate, decreased oxalate), and vestibulectomy (rare)
  • vulvodynia: local moisturization, cold compresses, systemic nerve blocking therapy (amitriptyline, gabapentin), topical anesthetics, estrogen cream
  • pain clinic

Menopause
• see Family Medicine, FM42

Definitions
• lack of menses for 1 yr
• types of menopause
  • physiological; average age 51 yr (follicular atresia)
  • premature ovarian failure; before age 40 (autoimmune disorder, infection, Turner’s syndrome)
  • iatrogenic (surgical/radiation/chemotherapy)

Clinical Features
• associated with estrogen deficiency
  • vasomotor instability (tends to dissipate with time)
    • hot flushes/flashes, night sweats, sleep disturbances, formication, nausea, palpitations
  • urogenital atrophy involving vagina, urethra, bladder
    • dyspareunia, pruritus, vaginal dryness, bleeding, urinary frequency, urgency, incontinence
    • skeletal
    • osteoporosis, joint and muscle pain, back pain
  • skin and soft tissue
    • decreased breast size, skin thinning/loss of elasticity
  • psychological
    • mood disturbance, irritability, fatigue, decreased libido, memory loss

Investigations
• increased levels of FSH (>35 IU/L) on day 3 of cycle (if still cycling) and LH (FSH>LH)
• FSH level not always predictive due to monthly variation; use absence of menses for 1 yr to diagnose
• decreased levels of estradiol (later)

Treatment
• goal is for individual symptom management
  • vasomotor instability
    • HRT (first line), SSRIs, venlafaxine, gabapentin, propranolol, clonidine
    • acupuncture
  • vaginal atrophy
    • local estrogen: cream (Premarin*), vaginal suppository (VagiFem*), ring (Estring*)
    • lubricants (Replens*)
  • urogenital health
    • lifestyle changes (weight loss, bladder re-training), local estrogen replacement, surgery

Menopause Pathophysiology
Degenerating theca cells fail to react to endogenous gonadotropins (FSH, LH)
• Less estrogen is produced
• Decreased negative feedback on hypothalamic-pituitary-adrenal axis
• Increased FSH and adrenal axis
• Stromal cells continue to produce androgens as a result of increased LH stimulation
Hormone Replacement Therapy

- see Family Medicine, FM42
- primary indication is treatment of menopausal symptoms (vasomotor instability)
- keep doses low (e.g. 0.3 mg Premarin®) and duration of treatment short (<5 yr)

HRT Components

- estrogen
  - oral or transdermal (e.g. patch, gel)
  - transdermal preferred for women with hypertriglyceridemia or impaired hepatic function, smokers, and women who suffer from headaches associated with oral HRT
  - low-dose (preferred dose: 0.3 mg Premarin®/25 µg Estradot® patch, can increase if necessary)
- progestin
  - given in combination with estrogen for women with an intact uterus to prevent development of endometrial hyperplasia/cancer

Table 16. Examples of HRT Regimens

<table>
<thead>
<tr>
<th>HRT Regimen</th>
<th>Estrogen Dose</th>
<th>Progestin Dose</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unopposed Estrogen</td>
<td>CEE 0.625 mg PO OD</td>
<td>None</td>
<td>If no intact uterus</td>
</tr>
<tr>
<td>Standard-dose</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 2.5 mg PO OD, or micronized progesterone 100 mg PO OD</td>
<td>Withdrawal bleeding may occur in a spotty, unpredictable manner. Usually abates after 6-8 mo due to endometrial atrophy. Once patient has become amenorrheic on HRT, significant subsequent bleeding episodes require evaluation (endometrial biopsy)</td>
</tr>
<tr>
<td>Standard-dose Cyclic</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA 5-10 mg PO days 1-14 only, or micronized progesterone 200 mg PO OD days 1-14 only</td>
<td>Bleeding occurs monthly after day 14 of progestin (can continue for years). PMS-like symptoms (breast tenderness, fluid retention, headache, nausea) are more prominent with cyclic HRT</td>
</tr>
<tr>
<td>Pulsatile</td>
<td>CEE 0.625 mg PO OD</td>
<td>MPA low-dose</td>
<td>3 d on, 3 d off</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Estroderm®/Estradiol 0.05 mg/d or 0.1 mg/d Estralis®/Estradiol 140 µg/d or 250 µg/d</td>
<td>Estroderm®/MPA 2.5 mg PO OD Estralis®-NEA 50 µg/d</td>
<td>Use patch twice weekly. Can use oral progestins (Estroderm®) or Combined patches available (Estralis®)</td>
</tr>
<tr>
<td>Topical</td>
<td>Estrace® 2.4 g/d x 1-2 wk, 1 g/d maintenance Premarin® 0.5-2 g/d for 21 d then off 7 d for vaginal atrophy, 0.5 g/d for 21 d then off 7 d or twice/wk for dyspareunia Estragyn® 2.4 g/d</td>
<td>Crinone® 4% or 8% (45 or 90 mg applicator)</td>
<td>If simultaneously taking oral estrogen tablet, may need to adjust dosing. If intact uterus, also take progesterone</td>
</tr>
</tbody>
</table>

CEE = conjugated equine estrogen (e.g. Premarin®); MPA = medroxyprogesterone acetate (e.g. Provera®); NEA = norethindrone acetate
Consider lower dose regimens. PREMPRO® 0.45/1.5 (Premarin® 0.45 mg and Provera® 1.5 mg); Estrace® (topical 17β-estradiol) = 0.1 mg active ingredient/g; Premarin® (topical CEE) = 0.625 mg active ingredient/g; Estragyn® (topical estrone) = 1 mg active ingredient/g.
Side Effects of HRT
- abnormal uterine bleeding
- mastodynia – breast tenderness
- edema, bloating, heartburn, nausea
- mood changes (progesterone)
- can be worse in progesterone phase of combined therapy

Contraindications to HRT
- absolute
  - acute liver disease
  - undiagnosed vaginal bleeding
  - known or suspected uterine cancer/breast cancer
  - acute vascular thrombosis or history of severe thrombophlebitis or thromboembolic disease
  - cardiovascular disease
- relative
  - pre-existing uncontrolled HTN
  - uterine fibroids and endometriosis
  - familial hyperlipidemias
  - migraine headaches
  - family history of estrogen-dependent cancer
  - chronic thrombophlebitis
  - DM (with vascular disease)
  - gallbladder disease, hypertriglyceridemia, impaired liver function (consider transdermal estrogen)
  - fibrocystic disease of the breasts

WOMEN’S HEALTH INITIATIVE (launched in 1991)
- two non-randomized studies investigating health risks and benefits of HRT in healthy postmenopausal women 50-79 yr old
- continuous combined HRT (CEE 0.625 mg + MPA 2.5 mg OD) in 16,608 women with an intact uterus
- estrogen-alone (CEE 0.625 mg) in 10,739 women with a previous hysterectomy
- both arms of the trial were stopped early because of evidence of increased risk of breast cancer, stroke, PE, and CHD in the combined HRT arm, and increased risk of stroke with no CHD benefits in the estrogen-alone arm
- the apparent increase in CHD was in disagreement with results of previous observational trial
- results of the WHI study have since been challenged and revision of how CHD was diagnosed led to loss of statistical significance of the results
- benefits and risks reported as number of cases per 10,000 women each year

Table 17. HRT Benefits vs. Risks

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Symptoms: less frequent and severe with use of either combined or estrogen-alone HRT</td>
<td>Stroke: 8 additional cases with combined HRT, and 12 additional cases for estrogen alone (WHI)</td>
</tr>
<tr>
<td>Osteoporosis: 5 fewer cases of hip fractures and 47 fewer cases of all fractures with combined HRT; 6 fewer cases of hip fractures with estrogen alone</td>
<td>DVT/PE: 18 additional cases with combined HRT, and 9 additional cases for estrogen-alone (WHI)</td>
</tr>
<tr>
<td>Colon Cancer: 6 fewer cases with combined HRT (WHI)</td>
<td>CHD: 7 additional MIs with combined HRT (WHI); secondary analysis suggests greater absolute risk for women aged &gt; 70 yr and for women who start HRT &gt; 10 yr post-menopause</td>
</tr>
<tr>
<td>One additional case with estrogen-alone</td>
<td>Breast Cancer: 8 additional cases with combined HRT (WHI)</td>
</tr>
<tr>
<td></td>
<td>Risk only increased after &gt; 5 yr of combined HRT use; no increased risk for estrogen-alone</td>
</tr>
<tr>
<td></td>
<td>Dementia and Mild Cognitive Impairment: 50% greater risk of developing dementia in women taking estrogen-alone after age 65; risk is greater for women taking combined HRT; risk of developing dementia was reduced for women taking HRT before age 65</td>
</tr>
</tbody>
</table>
Pelvic Relaxation/Prolapse

Etiology
- relaxation, weakness, or defect in the cardinal and uterosacral ligaments which normally maintain the uterus in an anteflexed position and prevent it from descending through the urogenital diaphragm (i.e. levator ani muscles)
  - related to
    - vaginal childbirth
    - aging
    - decreased estrogen (post-menopause)
    - following pelvic surgery
    - increased intra-abdominal pressure (obesity, chronic cough, constipation, ascites, heavy lifting)
    - congenital (rarely)
    - ethnicity (Caucasian women > Asian or African women)
    - collagen disorders

GENERAL CONSERVATIVE TREATMENT
(for pelvic relaxation/prolapse and urinary incontinence)
- Kegel exercises
- local vaginal estrogen therapy
- vaginal pessary (intravaginal suspension disc)

Table 18. Pelvic Prolapse

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystocele (protrusion of bladder into the anterior vaginal wall)</td>
<td>Frequency, urgency, nocturia • Stress incontinence • Incomplete bladder emptying • associated increased incidence of urinary tract infections – may lead to renal impairment</td>
<td>• See above • Anterior colporrhaphy (“anterior repair”) • Consider additional/alternative surgical procedure if documented urinary stress incontinence</td>
</tr>
<tr>
<td>Enterocele (protrusion of small bowel in upper posterior vaginal wall)</td>
<td>• Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated</td>
<td>• Similar to hemia repair • Contents reduced, neck of peritoneal sac ligated, uterosacral ligaments, and levator ani muscles approximated</td>
</tr>
<tr>
<td>Rectocele (protrusion of rectum into posterior vaginal wall)</td>
<td>Straining/digitation to evacuate stool • Constipation</td>
<td>• See above • Also laxatives and stool softeners • Posterior colporrhaphy (“posterior repair”), plication of endopelvic fascia and perineal muscles approximated in midline to support rectum and perineum (can result in dyspareunia)</td>
</tr>
</tbody>
</table>

Grading of Pelvic Organ Prolapse
- 0 = no descent during straining
- 1 = distal portion of prolapse >1 cm above level of hymen
- 2 = distal portion of prolapse ≤1 cm above or below level of hymen
- 3 = distal portion of prolapse >1 cm below level of hymen but without complete vaginal eversion
- 4 = complete eversion of total length of lower genital tract

Procidentia: failure of genital supports and complete protrusion of uterus through the vagina

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The only true hernia of the pelvis is an ENTROCELE because peritoneum herniates with the small bowel
Urinary Incontinence

- see Urology, U5

STRESS INCONTINENCE

Definition
- involuntary loss of urine with increased intra-abdominal pressure (coughing, laughing, sneezing, walking, running)

Risk Factors for Stress Incontinence in Women
- pelvic prolapse
- pelvic surgery
- vaginal delivery
- hypoestrogenic state (post-menopause)
- age
- smoking
- neurological/pulmonary disease

Treatment
- see General Conservative Treatment, GY37
- surgical
  - tension-free vaginal tape (TVT), tension-free obturator tape (TOT), prosthetic/fascial slings or retropubic bladder suspension (Burch or Marshall-Marchetti-Krantz procedures)

URGE INCONTINENCE

Definition
- urine loss associated with an abrupt, sudden urge to void
  - “overactive bladder”
  - diagnosed based on symptoms

Etiology
- idiopathic (90%)
- detrusor muscle overactivity (“detrusor instability”)

Associated Symptoms
- frequency, urgency, nocturia, leakage

Treatment
- behaviour modification (reduce caffeine/liquid, smoking cessation, regular voiding schedule)
- Kegel exercises
- medications
  - anticholinergics: oxybutinin (Ditropan®), tolterodine (Detrol®), solifenacin (VESIcare®)
  - tricyclic antidepressants: imipramine

Rule Out Neurological Causes of Urge Incontinence
- MS
- Herniated disc
- DM
ENDOMETRIAL CARCINOMA

Epidemiology
- most common gynecological malignancy in North America (40%); 4th most common cancer in women
- 2-3% of women develop endometrial carcinoma during lifetime
- mean age is 60 yr
- majority are diagnosed in early stage due to detection of symptoms
- 85-90% 5 yr survival for stage I disease
- 70-80% overall 5 yr survival for all stages

Risk Factors
- Type I: excess estrogen (estrogen unopposed by progesterone)
  - obesity
  - PCOS
  - unbalanced HRT (balanced HRT is protective)
  - late menopause
  - estrogen-producing ovarian tumours (e.g. granulosa cell tumours)
  - HNPCC (hereditary non-polyposis colorectal cancer)/Lynch II syndrome
  - tamoxifen
- Type II: not estrogen-related
  - possibly tamoxifen

Classification and Clinical Features
- Type I (well-differentiated endometrioid adenocarcinoma) ~80% of cases
  - postmenopausal bleeding in majority, abnormal uterine bleeding in majority of affected premenopausal women (menorrhagia, intermenstrual bleeding)
- Type II (serous, clear cell carcinoma, grade 3 endometrioid, undifferentiated, carcinosarcoma) ~15% of cases
  - may not present with bleeding in early stage, more likely to present with advanced stage disease with symptoms like ovarian cancer (i.e. bloating, bowel dysfunction, pelvic pressure)

Investigations
- endometrial sampling
  - office endometrial biopsy
  - D&C ± hysteroscopy
- ± pelvic ultrasound (in women where adequate endometrial sampling not feasible without invasive methods)
- ± not acceptable as alternative to pelvic exam or endometrial sampling to rule out cancer

Table 19. FIGO Staging of Endometrial Cancer (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIA</td>
<td>Invasion of serosa, corpus uteri ± adnexae</td>
<td>IIC</td>
<td>Metastasis to pelvic ± para-aortic LNs</td>
</tr>
<tr>
<td>IIB</td>
<td>Vaginal ± parametrial involvement</td>
<td>IIC1</td>
<td>Positive pelvic LN</td>
</tr>
<tr>
<td>IIBa</td>
<td>Invasion of bladder ± bowel mucosa</td>
<td>IIC2</td>
<td>Positive para-aortic LN ± positive pelvic LNs</td>
</tr>
<tr>
<td>IVA</td>
<td>Invasive metastases</td>
<td>IV</td>
<td>Invasion of bladder ± bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant mets, including intra-abdominal mets ± inguinal LNs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

FIGO: International Federation of Gynecology and Obstetrics
*Note: endocervical glandular involvement is now considered as Stage I (previously Stage II)

Spread
- direct extension is most common
- lymphatic spread to pelvic and para-aortic nodes
- transtubal dissemination to peritoneal cavity
- hematogenous spread (usually to lungs, liver)

Treatment
- surgical: hysterectomy/bilateral salpingo-oophorectomy (BSO) and pelvic washings ± pelvic and para-aortic node dissection ± omentectomy
- goals: diagnosis, staging, treatment, defining optimal adjuvant treatment
- laparoscopic approach associated with improved quality of life (optimal for most patients)
• adjuvant radiotherapy (for improved local control in patients at risk for local recurrence) and adjuvant chemotherapy (in patients at risk for distant recurrence or with metastatic disease): based on presence of poor prognostic factors in definitive pathology
• chemotherapy: often used for recurrent disease (especially if high grade or aggressive histology)
• hormonal therapy: progestins can be used for recurrent disease (especially if low grade)

UTERINE SARCOMA
• rare; 2-6% of all uterine malignancies
• arise from stromal components (endometrial stroma, mesenchymal or myometrial tissues)
• behave more aggressively and are associated with worse prognosis than endometrial carcinoma; 5-yr survival is 35%
• vaginal bleeding is most common presenting symptom

Table 20. Summary of Uterine Sarcoma Subtypes and Features

<table>
<thead>
<tr>
<th>Type</th>
<th>Epidemiology</th>
<th>Features</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>PURE TYPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Leiomyosarcoma</td>
<td>• Accounts for 40%</td>
<td>• Histologic distinction from leiomyoma 1. Increased mitotic count (&gt;10 mitoses/10 high power fields) 2. Tumour necrosis 3. Cellular atypia • Rapidly enlarging fibroids in a pre-menopausal woman • Enlarging fibroids in a postmenopausal woman</td>
<td>• Often post-operatively after uterus removed for presumed fibroids • Staging using FIGO 2009 staging for leiomyosarcomas</td>
<td>• Hysterectomy/BSO usually • No routine pelvic lymphadenectomy • Adjuvant chemotherapy may be used if tumour has spread beyond uterus, for palliation • Radiation therapy does not improve local control or survival • Poor outcomes overall, even for early stage disease</td>
</tr>
<tr>
<td>2. Endometrial Stromal Sarcoma (ESS)</td>
<td>• Accounts for 10-15% • Usually presents in perimenopausal or postmenopausal women with abnormal uterine bleeding</td>
<td>• Abnormal uterine bleeding • Good prognosis</td>
<td>• Diagnosed by histology of endometrial biopsy or D&amp;C • Staging using FIGO 2009 staging for ECC and adenosarcoma</td>
<td>• Hysterectomy/BSO (remove ovaries as ovarian hormones may stimulate growth) • No routine pelvic lymphadenectomy • Adjuvant therapy based on stage and histologic features (hormones and/or radiation) • Hormonal therapy (progestins) may be used for metastatic disease • Treatment primarily surgical • Radiation and/or chemotherapy for advanced disease or unresectable disease</td>
</tr>
<tr>
<td>3. Undifferentiated Sarcoma</td>
<td>• Accounts for 5-10%</td>
<td>• Severe nuclear pleomorphism, high mitotic activity, tumour cell necrosis, and lack smooth muscle or endometrial stromal differentiation • Poor prognosis</td>
<td>• Often found incidentally post-operatively for abnormal bleeding</td>
<td>• Treatment primarily surgical • Radiation and/or chemotherapy for advanced disease or unresectable disease</td>
</tr>
<tr>
<td>MIXED TYPE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Adenosarcoma</td>
<td>• The rarest of the uterine sarcoma • Mixed tumour of low malignant potential</td>
<td>• Present with abnormal vaginal bleeding • Polyloid mass in uterine cavity</td>
<td>• Mixture of benign epithelium with malignant low-grade sarcoma • Often found incidentally at time of hysterectomy for PMB</td>
<td>• Treatment is surgical with TAH/BSO</td>
</tr>
<tr>
<td>RECLASSIFIED</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Carcinosarcoma</td>
<td>• Most common (43%) • Recently reclassified as high grade endometrioid carcinoma with associated metaplasia of the mesenchyme, rather than arising separately from stroma • Surgical staging using FIGO 2009 staging for endometrial cancer</td>
<td>• Both epithelial and stromal malignant elements present • Tend to form bulky polyloid masses that often fill uterine cavity and extend into or through the endocervical canal – often have extraterine disease at presentation</td>
<td>• Diagnosed by histology of endometrial biopsy or D&amp;C</td>
<td>• Usually treated as “high grade endometrial carcinoma” since behaviour and treatment similar (i.e. surgical staging and resection of any gross metastatic disease, adjuvant chemotherapy and radiation)</td>
</tr>
</tbody>
</table>

Table 21. FIGO Staging of Uterine Sarcoma (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Tumour limited to uterus</td>
<td>IIIA</td>
<td>Tumour invades abdominal tissues, one site</td>
</tr>
<tr>
<td>IA</td>
<td>&lt;5 cm</td>
<td>IIIB</td>
<td>Metastasis to pelvic and/or para-aortic lymph nodes</td>
</tr>
<tr>
<td>IB</td>
<td>&gt;5 cm</td>
<td>IIC</td>
<td>Tumour invades bladder and/or rectum</td>
</tr>
<tr>
<td>II</td>
<td>Tumour extends beyond uterus</td>
<td>IV</td>
<td>Tumour invades bladder and/or rectum</td>
</tr>
<tr>
<td>IIA</td>
<td>To the pelvis, adnexal involvement</td>
<td>IVA</td>
<td>Distant metastasis</td>
</tr>
<tr>
<td>IIB</td>
<td>To extra-uterine pelvic tissue</td>
<td>IVB</td>
<td>Distant metastasis</td>
</tr>
</tbody>
</table>
Ovary

BENIGN OVARIAN TUMOURS
- see Table 22
- many are asymptomatic
- usually enlarge slowly, if at all
- may rupture or undergo torsion, causing pain
  - pain associated with torsion of an adnexal mass usually originates in the iliac fossa and radiates to the flank
- peritoneal irritation may result from an infarcted tumour – rare

MALIGNANT OVARIAN TUMOURS
- see Table 22

Epidemiology
- lifetime risk 1.4% (1/70)
- in women >50 yr, more than 50% of ovarian tumours are malignant
- causes more deaths in North America than all other gynecologic malignancies combined
- 4\textsuperscript{th} leading cause of cancer death in women
- 65% epithelial; 35% non-epithelial
- 5-10% of epithelial ovarian cancers are related to hereditary predisposition

Risk Factors (for epithelial ovarian cancers)
- excess estrogen
  - nulliparity
- early menarche/late menopause
- age
- family history of breast, colon, endometrial, ovarian cancer
- race: Caucasian

Protective Factors (for epithelial ovarian cancers)
- OCP: likely due to ovulation suppression (significant reduction in risk even after 1 yr of use)
- pregnancy/breastfeeding
- salpingectomy (prophylactic)
- hysterectomy (without removal of ovaries)
- BSO (prophylactic surgery performed for this reason in high risk women – i.e. BRCA mutation carriers)

Screening
- no effective method of mass screening
- routine CA-125 level measurements or U/S not recommended
  - high false positive rates
- controversial in high risk groups: transvaginal U/S and CA-125, starting age 30 (no consensus on interval)
- familial ovarian cancer (>1 first degree relative affected, BRCA-1 mutation)
- other cancers (e.g. endometrial, breast, colon)
- BRCA-1 or BRCA-2 mutation: may recommend prophylactic bilateral oophorectomy after age 35 or when child-bearing is completed

Clinical Features
- most women with epithelial ovarian cancer present with advanced stage disease since often “asymptomatic” until disseminated disease (symptoms with early stage disease are vague and non-specific)
  - when present, symptoms may include
    - abdominal symptoms (nausea, bloating, dyspepsia, anorexia, early satiety)
    - symptoms of mass effect
      - increased abdominal girth – from ascites or tumour itself
      - urinary frequency
      - constipation
    - postmenopausal bleeding; irregular menses if pre-menopausal (rare)

Low Malignant Potential (also called “Borderline”) Tumours
- pregnancy, OCP, and breastfeeding are protective factors
- ~15% of all epithelial ovarian tumours
- tumour cells display malignant characteristics histologically, but no invasion is identified
- able to metastasize, but not commonly
- treated primarily with surgery (BSO/omental biopsy ± hysterectomy)
- NO proven benefit of chemotherapy
- generally slow growing, excellent prognosis
  - 5 yr survival >99%
  - recurrences tend to occur late, may be associated with low grade serous carcinoma

Ovaries are like GEMS
- Germ-cell
- Epithelial
- Metastatic
- Sex cord stromal

Most (70%) epithelial ovarian cancers present at stage III disease

Risk/Protective Factors for Epithelial Ovarian Cancer
- NO CHILD
- Nulliparity
- OCP, breastfeeding, tubal ligation, hysterectomy (protective)
- Caucasian
- Family History
- Increasing age (>40 yr)
- Late menopause
- Delayed child-bearing

Ovarian Tumour Markers
- Epithelial cell – CA-125
- Stromal
  - Granulosa cell – inhibin
  - Sertoli-Leydig – androgens
- Germ cell
  - Dysgerminoma – LDH
  - Yolk sac – AFP
- Choriocarcinoma – \( \beta \)-hCG
- Immature Teratoma – none
- Embryonal cell – AFP + \( \beta \)-hCG

Diagnosis of ovarian tumours requires surgical pathology

Omental Cake: a term for ascites plus a fixed upper abdominal and pelvic mass; almost always signifies ovarian cancer

Malignant Ovarian Tumour Prognosis
5 Year Survival
- Stage I 75-95%
- Stage II 60-75%
- Stage III 23-41%
- Stage IV 11%
# Table 22. Ovarian Tumours

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FUNCTIONAL TUMOURS (all benign)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Follicular Cyst</td>
<td>Follicle fails to rupture during ovulation</td>
<td>Usually asymptomatic</td>
<td>4-8 cm mass, unilocular, lined with granulosa cells</td>
<td>Symptomatic or suspicious masses warrant surgical exploration. Otherwise if &lt; 6 cm, wait 6 wk then re-examine as cyst usually regresses with next cycle. OCP (ovarian suppression) – will prevent development of new cysts. Treatment usually laparoscopic (cystectomy vs. oophorectomy, based on fertility choice).</td>
</tr>
<tr>
<td>Lutein Cyst</td>
<td>Corpus luteum fails to regress after 14 d, becoming cystic or hemorrhagic</td>
<td>More likely to cause pain than follicular cyst May delay onset of next period</td>
<td>Larger (10-15 cm) and firmer than follicular cysts</td>
<td>Same as for follicular cysts</td>
</tr>
<tr>
<td>Theca-Lutein Cyst</td>
<td>Due to atretic follicles stimulated by abnormal β-hCG levels</td>
<td>Associated with molar pregnancy, ovulation induction with clomiphene</td>
<td>Conservative</td>
<td>Cyst will regress as β-hCG levels fall</td>
</tr>
<tr>
<td>Endometrioma</td>
<td>See Endometriosis, GY13</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polycystic Ovaries</td>
<td>See Polycystic Ovarian Syndrome, GY25</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>BENIGN GERM-CELL TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benign Cyst Teratoma (dermoid)</td>
<td>Single most common ovarian germ cell neoplasm Elements of all 3 cell lines; contains dermal appendages (sweat and sebaceous glands, hair follicles, teeth)</td>
<td>May rupture, twist, infarct 20% bilateral 20% occur outside of reproductive yr</td>
<td>Smooth-walled, mobile, unilocular Ultrasound may show calcification which is pathognomonic</td>
<td>Treatment usually laparoscopic cystectomy; may recur</td>
</tr>
<tr>
<td><strong>MALIGNANT GERM-CELL TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Rapidly growing, 2-3% of all ovarian cancers</td>
<td>Usually children and young women (&lt;30 yr)</td>
<td>Surgical resection (often conservative unilateral salpingo-oophorectomy ± nodes) ± chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Dysgerminoma</td>
<td>Produces LDH</td>
<td>10% bilateral</td>
<td>Usually very responsive to chemotherapy, therefore complete resection is not necessary for cure</td>
<td></td>
</tr>
<tr>
<td>Immature Teratoma</td>
<td>No tumour marker identified</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>EPITHELIAL OVARIAN TUMOURS (malignant or borderline)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td>Derived from mesothelial cells lining peritoneal cavity Classified based on histologic type 80-85% of all ovarian neoplasms (includes malignant)</td>
<td>Varies depending on subtype</td>
<td>Cystectomy vs. unilateral salpingo-oophorectomy</td>
<td></td>
</tr>
<tr>
<td>Serous</td>
<td>Most common ovarian tumour 50% of all ovarian cancers 75% of epithelial tumours 70% benign</td>
<td>20-30% bilateral</td>
<td>Lining similar to fallopian tube epithelium Often multicellular Histologically contain Psammoma bodies (calcified concentric concretions)</td>
<td>Malignant 1. Early stage (stage II): Hysterectomy/BSO/staging (omentectomy, peritoneal biopsies, washings, pelvic and para-aortic lymphadenectomy) 2. Advanced stage: Upfront cytoreductive (debulking) followed by adjuvant chemotherapy consisting of IV carboplatin/paclitaxel vs. intraperitoneal chemotherapy (stage III) neoadjuvant chemotherapy with IV carboplatina/paclitaxel, followed by delayed debulking with further adjuvant IV chemotherapy</td>
</tr>
<tr>
<td>Mucinous</td>
<td>20% of epithelial tumours 85% benign</td>
<td>Rarely complicated by Pseudomyxoma peritonei: implants seed abdominal cavity and produce large quantities of mucin</td>
<td>Resembles endocervical epithelium Often multicellular May reach enormous size</td>
<td>Poor response to chemotherapy if mucinous, remove appendix as well to rule out possible source of primary disease</td>
</tr>
<tr>
<td><strong>EPITHELIAL OVARIAN TUMOURS (malignant or borderline)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Table 22. Ovarian Tumours (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
<th>Presentation</th>
<th>Ultrasound/Cytology</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SEX CORD STROMAL OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Information</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibroma/Thecoma (benign)</td>
<td>From mature fibroblasts in ovarian stroma</td>
<td>Non-functioning Occasionally associated with Meig’s syndrome (benign ovarian tumour and ascites and pleural effusion)</td>
<td>Firm, smooth rounded tumour with interfacing fibrinocytes</td>
<td>Surgical resection of tumour Chemotherapy may be used for unresectable metastatic disease</td>
</tr>
<tr>
<td>Granulosa-Thecoma Cell Tumours (benign or malignant)</td>
<td>Can be associated with endometrial cancer Inhibin is tumour marker</td>
<td>Estrogen-producing → feminizing effects (precocious puberty, menorrhagia, postmenopausal bleeding)</td>
<td>Histologic hallmark of cancer is small groups of cells known as Call-Exner bodies</td>
<td></td>
</tr>
<tr>
<td>Sertoli-Leydig Cell Tumour (benign or malignant)</td>
<td>Can measure elevated androgens as tumour markers</td>
<td>Androgen-producing → virilizing effects (hirsutism, deep voice, recession of front hairline)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>METASTATIC OVARIAN TUMOURS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From GI Tract, Breast, Endometrium, Lymphoma</td>
<td>4-8% of ovarian malignancies Krukenberg tumour – metastatic ovarian tumour (usually GI tract, commonly stomach or colon, breast) with “signet-ring” cells</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Investigation of Suspicious Ovarian Mass

- women with suspected ovarian cancer based on history, physical, or investigations should be referred to a gynecologic oncologist
  - bimanual examination
  - solid, irregular, or fixed pelvic mass is suggestive of ovarian cancer
  - RMI (Risk of Malignancy Index) is best tool available to assess likelihood of ovarian malignancy and need for pre-operative gynecologic oncology referral (see sidebar, GY44)
  - blood work: CA-125 for baseline, CBC, liver function tests, electrolytes, creatinine
  - radiology
    - bone scan or PET scan not indicated
    - transvaginal ultrasound best to visualize ovaries
    - CT scan abdomen and pelvis to look for metastatic disease
  - try to rule out other primary source if suspected, based on
    - occult blood per rectum: endoscopy ± barium enema
    - gastric symptoms, gastroscopy ± upper GI series
    - abnormal vaginal bleeding, endometrial biopsy to rule out concurrent endometrial cancer
    - colposcopy ± ECC to rule out cervical cancer if abnormal cervix
    - breast lesion identified or risk factors present: mammogram

Table 23. FIGO Staging for Primary Carcinoma of the Ovary (Surgical Staging) (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Growth limited to the ovaries</td>
</tr>
<tr>
<td>IA</td>
<td>1 ovary, no ascites, no tumour on external surface, capsule intact</td>
</tr>
<tr>
<td>IB</td>
<td>2 ovaries, no ascites, no tumour on external surface, capsule intact</td>
</tr>
<tr>
<td>IC</td>
<td>1 or 2 ovaries with any of the following: capsule ruptured, tumour on ovarian surface, or malignant cells in ascites</td>
</tr>
<tr>
<td>II</td>
<td>Growth involving one or both ovaries with pelvic extension</td>
</tr>
<tr>
<td>IIA</td>
<td>Extension ± metastases to uterus/tubes</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension to other pelvic structures</td>
</tr>
<tr>
<td>IIC</td>
<td>II A/B with malignant cells in ascites or positive peritoneal washings</td>
</tr>
<tr>
<td>III</td>
<td>Tumour involving one or both ovaries with peritoneal implants outside the pelvis and/or positive retroperitoneal or intraperitoneal nodes; superficial liver mets is Stage III</td>
</tr>
<tr>
<td>IIIA</td>
<td>Microscopic peritoneal metastasis beyond pelvis, LNs negative</td>
</tr>
<tr>
<td>IIIB</td>
<td>Macroscopic peritoneal metastasis beyond pelvis - &lt;2 cm, LNs negative</td>
</tr>
<tr>
<td>IIIC</td>
<td>Implant - &gt;2 cm and/or retroperitoneal or intraperitoneal nodes</td>
</tr>
<tr>
<td>IV</td>
<td>Distant metastasis beyond peritoneal cavity</td>
</tr>
</tbody>
</table>

FIGO = International Federation of Gynecology and Obstetrics
Cervix

BENIGN CERVICAL LESIONS
- Nabothian cyst/inclusion cyst
  - no treatment required
- endocervical polyps
  - treatment is polypectomy (office procedure)

MALIGNANT CERVICAL LESIONS

Epidemiology
- majority are SCC (95%); adenocarcinomas increasing (5%); rare subtypes include small cell, adenosquamous
- 8,000 deaths annually in North America
- annual Pap test reduces a woman's chance of dying from cervical cancer from 0.4% to 0.05%
- average age at presentation: 52 yr old

Etiology
- at birth, vagina is lined with squamous epithelium; columnar epithelium lines only the endocervix and the central area of the ectocervix (original squamocolumnar junction)
- during puberty, estrogen stimulates eversion of a single columnar layer (ectopy), thus exposing it to the acidic pH of the vagina, leading to metaplasia (change of exposed epithelium from squamous to columnar)
  - a new squamocolumnar junction forms as a result
- the transformation zone (TZ) is the area located between the original and the current squamocolumnar junction
- the majority of dysplasias and cancers arise in the TZ of the cervix
- must have active metaplasia in presence of inducing agent (HPV) to get dysplasia
dysplasia → carcinoma in situ (CIS) → invasion
- slow process (~10 yr on average)
- growth is by local extension
- metastasis occurs late

Risk Factors
- HPV infection
  - see Sexually Transmitted Infections, GY28
  - high risk of neoplasia associated with types 16, 18
  - low risk of neoplasia associated with types 6, 11
  - >99% of cervical cancers contain one of the high risk HPV types
- high risk behaviours (risk factors for HPV infection)
  - multiple partners
  - other STIs (HSV, trichomonas)
  - early age at first intercourse
  - high risk male partner
- smoking
- poor screening uptake is the most important risk factor for cervical cancer in Canada
- at-risk groups include
  - immigrant Canadians
  - First Nations Canadians
  - geographically isolated Canadians
  - sex-trade workers
  - low socioeconomic status

Cervical Cancer Screening Guidelines (Pap Test)
- see Family Medicine, FM4

Clinical Features
- SCC: exophytic, fungating tumour
- adenocarcinoma: endophytic, with barrel-shaped cervix
- early
  - asymptomatic
  - discharge: initially watery, becoming brown or red
  - postcoital bleeding
- late
  - 80-90% present with bleeding: either postcoital, postmenopausal or irregular bleeding
  - pelvic or back pain (extension of tumour to pelvic walls)
  - bladder/bowel symptoms
- signs
  - friable, raised, reddened, or ulcerated area visible on cervix

A Risk of Malignancy Incorporating CA125, Ultrasound, and Menopausal Status for the Accurate Pre-Operative Diagnosis of Ovarian Cancer
BJOG 1990;97:922-929
RMI = U x M x CA-125

Ultrasound Findings (1 pt for each)
- Multilocular cyst
- Evidence of solid areas
- Evidence of metastases
- Presence of ascites
- Bilateral lesions
U = 1 (for U/S scores of 0 or 1)
U = 4 (for U/S scores of 2-5)

Menopausal Status
- Postmenopausal: M = 4
- Premenopausal: M = 1

Absolute Value of CA-125 Serum Level
- For RMI>200: Gynecologic oncology referral is recommended

Cervical cancer is most prevalent in developing countries and therefore is the only gynecologic cancer that uses clinical staging; this facilitates consistent international staging with countries that do not have technologies, such as CT and MRI

The Bethesda Classification System is based on cytological results of a Pap test that permits the examination of cells but not tissue structure. Cervical intraepithelial neoplasia (CIN) or cervical carcinoma is a histological diagnosis, requiring a tissue sample via biopsy of suspicious lesions seen during colposcopy.

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease.
Figure 22. Decision making chart for Pap test (not applicable for adolescents)
Adapted from: Ontario Cervical Screening Practice Guidelines. May 2012. Cervical screening guidelines unique to each province

Diagnosis
- apply acetic acid and identify acetowhite lesions, punctuation, mosaicism, and abnormal blood vessels to guide cervical biopsy
- endocervical curettage (ECC) if entire lesion is not visible or no lesion visible
- diagnostic excision (LEEP) if
  - lesion extends into endocervical canal
  - positive ECC
  - discrepancy between Pap test results and colposcopy
  - microinvasive carcinoma
- consider cold knife conization (in OR) if glandular abnormality suspected based on cytology or colposcopic findings due to concern for margin interpretation
- tests permitted for FIGO clinical staging include: physical exam (including EUA), cervical biopsy (including cone biopsy), proctoscopy/cystoscopy, IVP, ultrasound liver/kidneys, CXR, LFTs
- MRI and/or CT and/or PET scan often done to facilitate planning of radiation therapy, results do not influence clinical stage

Table 24. FIGO Staging Classification of Cervical Cancer (Clinical Staging) (2009)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Confined to cervix</td>
</tr>
<tr>
<td>IA</td>
<td>Microinvasive (diagnosed only by microscopy)</td>
</tr>
<tr>
<td>IB</td>
<td>Clinically visible lesion confined to cervix, or microscopic lesion &gt;IA</td>
</tr>
<tr>
<td>IIA</td>
<td>Stromal invasion not &gt; 3 mm deep, not &gt;7 mm wide</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion ≤4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIC</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>II</td>
<td>Beyond uterus but not to the pelvic wall or lower 1/3 of vagina</td>
</tr>
<tr>
<td>IIA</td>
<td>Clinically visible lesion ≤4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIA</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIB</td>
<td>Obvious parametrical involvement</td>
</tr>
<tr>
<td>III</td>
<td>Extends to pelvic wall, and/or involves lower 1/3 of vagina and/or causes hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IIIA</td>
<td>Clinically visible lesion &gt;4 mm in greatest dimension</td>
</tr>
<tr>
<td>IIA</td>
<td>Involves lower 1/3 vagina but no extension into pelvic side wall</td>
</tr>
<tr>
<td>IIB</td>
<td>Extension into pelvic side wall and/or hydronephrosis or non-functioning kidney</td>
</tr>
<tr>
<td>IV</td>
<td>Carcinoma has extended beyond true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum</td>
</tr>
<tr>
<td>IVA</td>
<td>Spread of the growth to adjacent organs</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases</td>
</tr>
</tbody>
</table>

Treatment: Prevention and Management

Prevention: HPV Vaccine
- two vaccines currently approved (Gardasil®, Cervarix®)
• should be administered before onset of sexual activity (i.e. before exposure to virus) for optimal benefit of vaccination
• may be given at the same time as hepatitis B or other vaccines using a different injection site
• not for treatment of active infections
• most women will not be infected with all four types of the virus at the same time, therefore vaccine is still indicated for sexually active females or those with a history of previous HPV infection or HPV-related disease
• conception should be avoided until 30 d after last dose of vaccination

### Table 25. Comparison of Two Vaccines against Human Papillomavirus (HPV)

<table>
<thead>
<tr>
<th></th>
<th>Gardasil®</th>
<th>Cervarix®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viral strains covered</td>
<td>6, 11, 16, 18</td>
<td>16, 18</td>
</tr>
<tr>
<td>Route of administration</td>
<td>IM</td>
<td>IM</td>
</tr>
<tr>
<td>Schedule of dosing</td>
<td>0, 2, 6 mo</td>
<td>0, 1, 6 mo</td>
</tr>
<tr>
<td>Side effects</td>
<td>Local: redness, pain, swelling</td>
<td>Local: redness, pain, swelling</td>
</tr>
<tr>
<td></td>
<td>General: headache, low grade fever, GI upset</td>
<td>General: headache, low grade fever, GI upset</td>
</tr>
<tr>
<td>Approved age</td>
<td>Females age 9-45, males age 9-26</td>
<td>Females age 10-25</td>
</tr>
<tr>
<td>Contraindications</td>
<td>Pregnant women and women who are nursing (limited data)</td>
<td></td>
</tr>
</tbody>
</table>

*Gardasil® also covers types 31, 33, 45, 52, and 58; also used to prevent genital warts

### Table 26. Management of Patients Abnormal Cervical Histology and Cervical Cancer

#### Management

**CIN I**
- Preferred option for biopsy-proven CIN I is observation
- Repeat assessment and cytology in T2 mo
- Management according to cytology results
- If after HSIL or AGC
- Cytology and histology should be reviewed
- If discrepancy remains, excisional biopsy may be considered

**CIN II and CIN III**
- Women ≥25 yr
- CIN II or III should be treated
- Excisional procedures preferred for CIN III
- Those with positive margins should have follow-up with colposcopy and directed biopsies and/or endocervical curettage
- Treatment for recurrent CIN II or III should be by excision
- Women <25 yr
- Cytology and histology should be reviewed
- If discrepancy remains, excisional biopsy may be considered

**Stage IA1** (no LVSI)
- Trachelectomy (removal of only the cervix) if future fertility desired (and lesion ≤2 cm)
- Simple hysterectomy if future fertility is not desired

**Stage IA2, IB1**
- Typically treated with radical hysterectomy and pelvic lymphadenectomy (sentinel nodes under study)
- Equal cure rates may be obtained with primary radiation therapy; advantage of surgery: may accurately stage and grade and more targeted adjuvant therapy
- Advantages is that ovaries can be spared if pre-menopausal
- For fertility preservation, may have radical trachelectomy (removal of cervix and parametria) and nodes instead of radical hysterectomy for early-stage disease
- Concurrent chemoradiation therapy if adverse high risk prognostic factors on radical surgical specimen, such as: positive pelvic lymph nodes, positive parametria, and/or positive margins

**Stages IB2 (4 cm), II, III, IV**
- Primary chemoradiation therapy
- PET/CT to grade: evaluate pelvic and para-aortic nodes
- For positive nodes on PET: primary chemoradiation with extended field RT
- Hysterectomy generally not suggested following primary treatment with curative intent

### Abnormal Pap Tests in Pregnancy

- incidence: 1/2,200
- Pap test at all initial prenatal visits
- if abnormal Pap or suspicious lesion, refer to colposcopy
- if diagnostic conization required, should be deferred until second trimester (T2) to minimize risk of pregnancy loss
- if invasive cancer ruled out, management of dysplasia deferred until completion of pregnancy (may deliver vaginally)
- if invasive cancer present, management depends on prognostic factors, degree of fetal maturity, and patient wishes
  - general recommendations in T1: consider pregnancy termination, management with either radical surgery (hysterectomy vs. trachelectomy if desires future fertility), or concurrent chemoradiation therapy
  - recommendations in T2/T3: delay of therapy until viable fetus and C/S for delivery with concurrent radical surgery or subsequent concurrent chemoradiation therapy

### Efficacy of Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine Against Cervical Infection and Precancer Caused by Oncogenic HPV Types (PATRICIA): Final Analysis of a Double-Blind, Randomized Study in Young Women

**Study:** Phase III double-blind, controlled RCT.

**Patients:** 18,644 women aged 15-25.

**Selected Outcomes:** Development of HPV-16/18 associated CIN II+, CIN III, and invasive cervical cancer was the primary outcome. Secondary to this were persistence of infections with HPV-16, HPV-18, or other oncogenic HPV types.

**Selected Results:** Efficacy against development of HPV-16/18 associated CIN II+ was 98.1% (p<0.0001). Low levels of cross-protection were observed for persistent infection with HPV-31 and HPV-45 and HPV-31 or HPV-45 associated CIN II+.

**Conclusions:** The HPV-16/18 AS04-adjuvanted vaccine protected against HPV-16/18 associated CIN II+ lesions and lesions associated with HPV-31, HPV-33, and HPV-45.

**References:**
- Randomized Study in Young Women
- Lancet 2009;374:301-314
Vulva

BENIGN VULVAR LESIONS

Non-Neoplastic Disorders of Vulvar Epithelium
- biopsy is necessary to make diagnosis and/or rule out malignancy
- hyperplastic dystrophy (squamous cell hyperplasia)
  - surface thickened and hyperkeratotic
  - pruritus most common symptom
  - typically postmenopausal women
  - treatment: 1% fluorinated corticosteroid ointment bid for 6 wk
- lichen sclerosis
  - subepithelial fat becomes diminished; labia become thin, atrophic, with membrane-like epithelium and labial fusion
  - pruritus, dyspareunia, burning
  - ‘figure of 8’ distribution
  - most common in postmenopausal women but can occur at any age
  - treatment: ultrapotent topical steroid 0.05% clobetasol x 2-4 wk then taper down, can consider long term suppression twice a week
- mixed dystrophy (lichen sclerosis with epithelial hyperplasia)
  - hyperkeratotic areas with areas of thin, shiny epithelium
  - treatment: fluorinated corticosteroid ointment

Tumours
- papillary hidradenoma, nevus, fibroma, hemangioma

MALIGNANT VULVAR LESIONS

Epidemiology
- 5% of genital tract malignancies
- 90% SCC; remainder melanomas, basal cell carcinoma, Paget's disease, Bartholin's gland carcinoma
  - Type I disease: HPV-related (50-70%)
    - more likely in younger women
    - 90% of VIN contain HPV DNA (usually types 16, 18)
  - Type II disease: not HPV-related, associated with current or previous vulvar dystrophy
    - usually postmenopausal women

Risk Factors
- HPV infection
- VIN: precancerous change which presents as multicentric white or pigmented plaques on vulva (may only be visible at colposcopy)
  - progression to cancer rarely occurs with appropriate management
  - treatment: local excision (i.e. superficial vulvectomy ± split thickness skin grafting to cover defects if required) vs. ablative therapy (i.e. laser, cauterization) vs. local immunotherapy (imiquimod)

Clinical Features
- many patients asymptomatic at diagnosis (many also deny or minimize symptoms)
- most lesions occur on the labia majora, followed by the labia minora (less commonly on the clitoris or perineum)
- localized pruritus or lesion most common
- less common: raised red, white or pigmented plaque, ulcer, bleeding, discharge, pain, dysuria
- patterns of spread
  - local
  - groin lymph nodes (usually inguinal → pelvic nodes)
  - hematogenous

Investigations
- ± colposcopy
- ALWAYS biopsy any suspicious lesion

Prognosis
- depends on stage – particularly nodal involvement (single most important predictor followed by tumour size)
- lesions >4 cm associated with poorer prognosis
- overall 5 yr survival rate: 79%
Vagina

BENIGN VAGINAL LESIONS

- inclusion cysts
  - cysts form at site of abnormal healing of laceration (e.g. episiotomy)
  - no treatment required
- endometriosis
  - dark lesions that tend to bleed at time of menses
  - treatment: excision
- Gartner's duct cysts
  - remnants of Wolffian duct, seen along side of cervix
  - treatment: conservative unless symptomatic
- urethral diverticulum
  - can lead to recurrent urethral infection, dyspareunia
  - treatment: surgical correction if symptomatic

MALIGNANT VAGINAL LESIONS

Epidemiology

- primary carcinomas of the vagina represent 2-3% of malignant neoplasms of the female genital tract
- 80-90% are SCC
- more than 50% diagnosed between 70-90 yr old

Risk Factors

- associated with HPV infection (analogous to cervical cancer)
- increased incidence in patients with prior history of cervical and vulvar cancer

Investigations

- cytology
  - significant false negative rate for existing malignancy (i.e. if gross lesion present, biopsy!)
- colposcopy
- Schiller test (normal squamous epithelium takes up Lugol's iodine)
- biopsy, partial vaginectomy (wide local excision for diagnosis)
- rule out disease on cervix, vulva, or anus (most vaginal cancers are actually metastatic from one of these sites)
- staging

Clinical Features

Table 27. Clinical Features of Malignant Vaginal Lesions

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal Intra-Epithelial Neoplasia (VAIN)</td>
<td>Grades: analogous to cervical dysplasia</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma (SCC)</td>
<td>Most common site is upper 1/3 of posterior wall of vagina</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic</td>
</tr>
<tr>
<td></td>
<td>Painless discharge and bleeding</td>
</tr>
<tr>
<td></td>
<td>Vaginal discharge (often foul-smelling)</td>
</tr>
<tr>
<td></td>
<td>Vaginal bleeding especially during/post-coitus</td>
</tr>
<tr>
<td></td>
<td>Urinary and/or rectal symptom 2° to compression</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>Most are metastatic, usually from cervix, endometrium, ovary, or colon</td>
</tr>
<tr>
<td></td>
<td>Most primaries are clear cell adenocarcinomas</td>
</tr>
<tr>
<td></td>
<td>2 types: non-DES and DES syndrome</td>
</tr>
</tbody>
</table>

Fallopian Tube

- least common site for carcinoma of female reproductive system (0.3%)
- usually serous epithelial carcinoma
- recently considered to be origin of serous ovarian cancer
- more common in fifth and sixth decade

Clinical Features

- classic triad present in minority of cases, but very specific
  - watery discharge (most specific) = "hydrops tubae profuens"
  - vaginal bleeding or discharge in 50% of patients
  - crampy lower abdominal/pelvic pain
- most patients present with a pelvic mass (see Ovarian Tumours, GY41 for guidelines regarding diagnosis/investigation)

Treatment

- as for malignant epithelial ovarian tumours
Gestational Trophoblastic Disease/Neoplasia

- refers to a spectrum of proliferative abnormalities of the trophoblast

Epidemiology
- 1/1,000 pregnancies
- marked geographic variation – as high as 1/125 in Taiwan
- 80% benign, 15% locally invasive, 5% metastatic
- cure rate >95%

HYDATIDIFORM MOLE (Benign GTD)

Complete Mole
- most common type of hydatidiform mole
- diffuse trophoblastic hyperplasia, hydropic swelling of chorionic villi, no fetal tissues, or membranes present
- 46XX or 46XY, chromosomes completely of paternal origin (90%)
- 2 sperm fertilize empty egg or 1 sperm with reduplication
- 15-20% risk of progression to malignant sequelae
- risk factors
  - geographic (South East Asia most common)
  - others (maternal age >40 yr, β-carotene deficiency, vitamin A deficiency) – not proven
- clinical features
  - often present during apparent pregnancy with abnormal symptoms/findings
    - vaginal bleeding (97%)
    - excessive uterine size for LMP (51%)
    - theca-lutein cysts >6 cm (50%)
    - preeclampsia (27%)
- β-hCG >100,000 IU/L

Partial (or Incomplete) Mole
- focal trophoblastic hyperplasia and hydropic villi are associated with fetus or fetal parts
- often triploid (XXY, XYY, XXX) with chromosome complement from both parents
  - usually related to single ovum fertilized by two sperm
- low risk of progression to malignant sequelae (<4%)
- associated with fetus, which may be growth-restricted, and/or have multiple congenital malformations
- clinical features
  - typically present similar to threatened/spontaneous/missed abortion
  - pathological diagnosis often made after D&C

Investigations
- quantitative β-hCG levels (tumour marker) abnormally high for gestational age
- U/S findings
  - if complete: no fetus (classic “snow storm” due to swelling of villi)
  - if partial: molar degeneration of placenta ± fetal anomalies, multiple echogenic regions corresponding to hydropic villi, and focal intrauterine hemorrhage
- CXR (may show metastatic lesions)
- features of molar pregnancies at high risk of developing persistent GTN post-evacuation
  - local uterine invasion as high as 31%
  - β-hCG >100,000 IU/L
  - excessive uterine size
  - prominent theca-lutein cysts

Treatment
- suction D&C with sharp curettage and oxytocin
- Rhogam® if Rh negative
- consider hysterectomy (if patient no longer desires fertility)
- prophylactic chemotherapy of no proven benefit
- chemotherapy for GTN if develops after evacuation

Follow-Up
- contraception required to avoid pregnancy during entire follow-up period
- serial β-hCGs (as tumour marker) every week until negative x 3 (usually takes several wk), then monthly for 6-12 mo prior to trying to conceive again
- increase or plateau of β-hCG indicates GTN → patient needs chemotherapy

With development of hypertension early in pregnancy (i.e. <20 wk), think gestational trophoblastic disease
GTN (MALIGNANT GTD)

Invasive Mole or Persistent GTN
- diagnosis made by rising or plateau in $\beta$-hCG, development of metastases following treatment of documented molar pregnancy
- histology: molar tissue from D&C
- metastases are rare (4%)

Choriocarcinoma
- often present with symptoms from metastases
- highly anaplastic, highly vascular
- no choriionic villi, elements of syncytiotrophoblast and cytotrophoblast
- may follow molar pregnancy, abortion, ectopic, or normal pregnancy

Placental-site Trophoblastic Tumour
- rare aggressive form of GTN
- abnormal growth of intermediate trophoblastic cells
- low $\beta$-hCG, production of human placental lactogen (hPL), relatively insensitive to chemotherapy

CLASSIFICATION of GTN
- non-metastatic
  - $\sim 15\%$ of patients after molar evacuation
  - may present with abnormal bleeding
  - all have rising or plateau of $\beta$-hCG
  - negative metastases on staging investigations
- metastatic
  - 4% patients after treatment of complete molar pregnancy
  - metastasis more common with choriocarcinoma which tends toward early vascular invasion and widespread dissemination
  - if signs or symptoms suggest hematogenous spread, do not biopsy (they bleed)
    - lungs (80%): cough, hemoptysis, CXR lesion(s)
    - vagina (30%): vaginal bleeding, "blue lesions" on speculum exam
    - pelvis (20%): rectal bleeding (if invades bowel), U/S lesion(s)
    - liver (10%): elevated LFTs, U/S or CT findings
    - brain (10%): headaches, dizziness, seizure (symptoms of space-occupying lesion), CT/MRI findings
  - highly vascular tumour $\rightarrow$ bleeding $\rightarrow$ anemia
  - all have rising or plateau of $\beta$-hCG
  - classification of metastatic GTN
    - divided into good prognosis and bad prognosis
    - features of bad prognosis
      - long duration (>4 mo from antecedent pregnancy)
      - high pre-treatment $\beta$-hCG titre: >100,000 IU/24 h urine or >40,000 IU/L of blood
      - brain or liver metastases
      - prior chemotherapy
      - metastatic disease following term pregnancy
    - good prognosis characterized by the absence of each of these features

Investigations – For Staging
- blood work: CBC, electrolytes, creatinine, $\beta$-hCG, TSH, LFTs
- imaging: CXR, U/S pelvis, CT abdo/pelvis, CT brain
- if suspect brain metastasis but CT brain negative, consider lumbar puncture for CSF $\beta$-hCG
- ratio of plasma $\beta$-hCG:CSF $\beta$-hCG <60 indicates metastases

Table 28. FIGO Staging and Management of Malignant GTN

<table>
<thead>
<tr>
<th>Stage</th>
<th>Findings</th>
<th>Management</th>
</tr>
</thead>
</table>
| I     | Disease confined to uterine corpus | Single agent chemotherapy for low risk disease (WHO score ≤6)  
  1st line: pulsed – actinomycin D (Act-D) IV q2wk  
  Alternatives: MTX-based regimen  
  20% of patients need to switch to alternate single-agent regimen due to failure of $\beta$-hCG to return to normal  
  Combination chemotherapy (EMA-CO: etoposide, MTX, ACT-D, cyclophosphamide, vincristine) if high risk (WHO score ≥7) or if resistant to single agent chemotherapy  
  Can consider hysterectomy if fertility not desired or placental-site trophoblastic tumour |
| II    | Metastatic disease to genital structures | As above |
| III   | Metastatic disease to lungs with or without genital tract involvement | As above |
| IV    | Distant metastatic sites including brain, liver, kidney, GI tract | Usually high risk (EMA-CO) with surgical resection of sites of disease  
  Persistence/resistance to chemotherapy  
  Consider radiation for brain mets |
### Table 29. WHO Prognostic Score for GTD (2011)

<table>
<thead>
<tr>
<th>Prognostic Factor</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal Age</td>
<td></td>
<td></td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP Mole Abortion Termined</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interval (end of AP to chemotherapy in months)</td>
<td></td>
<td>&lt;4</td>
<td>4-6</td>
<td>7-13</td>
<td>&gt;13</td>
</tr>
<tr>
<td>HCG IU/l</td>
<td></td>
<td></td>
<td>103-104</td>
<td>104-105</td>
<td>&gt;105</td>
</tr>
<tr>
<td>Number of Metastases</td>
<td></td>
<td></td>
<td>1-4</td>
<td>5-8</td>
<td>&gt;8</td>
</tr>
<tr>
<td>Site of Metastases</td>
<td></td>
<td>Lung</td>
<td>Spleen, kidney</td>
<td>Gl tract</td>
<td>Brain, liver</td>
</tr>
<tr>
<td>Largest Tumor Mass</td>
<td></td>
<td>3-5 cm</td>
<td>&gt;5 cm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prior Chemotherapy</td>
<td></td>
<td>Single drug</td>
<td>Two drug</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Follow-up (for GTN)
- contraception for all stages to avoid pregnancy during entire follow-up period
- stage I, II, III
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 12 mo
- stage IV
  - weekly β-hCG until 3 consecutive normal results
  - then monthly x 24 mo

### Common Medications

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
</table>
| acyclovir (Zovirax®)   | Antiviral; inhibits DNA synthesis and viral replication | First Episode: 400 mg PO tid x 7-10 d  
Recurrent: 400 mg PO tid x 5 d | Genital herpes | S/E: headache, GI upset  
D/I: zidovudine, probenecid |
| bromocriptine (Parlodel®) | Dopaminomimetic Agonist at D₂R  
Antagonist at D₁R | Initial: 1.25-2.5 mg PO qhs with food  
Then: increase by 2.5 mg every 2-7 d as needed until optimal therapeutic response  
Usual Range: 1.5-15 mg OD For IVF:  
Initial: 1.25 mg/d PO between days 4-6 of follicular phase  
Then: 2.5 mg/d until 3 d after onset menstruation | Galactorrhea + amenorrhea  
2° to hyperprolactinemia  
Prolactin-dependent menstrual disorders and infertility  
Prolactin-secreting adenomas (microadenomas, prior to surgery of macroadenomas) IVF | S/E: N/V, headache, postural hypotension, somnolence  
C/I: uncontrolled HTN, pregnancy-induced HTN, CAD, breastfeeding  
D/I: domperidone, macrolides, octreotide |
| clomiphene citrate (Clomid®) | Increases output of pituitary gonadotropins which induces ovulation | 50 mg OD x 5 d  
Try 100 mg or 160 mg OD if ineffective  
3 courses = adequate trial | Patients with persistent ovulatory dysfunction (e.g. amenorrhea, PCOS) who desire pregnancy | S/E: Common – hot flashes, abdominal discomfort, exaggerated cyclic ovarian enlargement, accentuation of Mittelschmerz  
Rare – ovarian hyperstimulation syndrome, multiple pregnancy, visual blurring, birth defects  
C/I: pregnancy, liver disease, hormone-dependent tumours, ovarian cyst, undiagnosed vaginal bleeding |
| clotrimazole (Canesten®) | Antifungal; disrupt fungal cell membrane | Tablet: 100 mg/d intravaginally x 7 d or 200 mg/d x 3 d or 500 mg x 1 dose  
Cream (1 or 2%): 1 applicator intravaginally qhs x 3-7 d  
Topical: apply bid x 7 d | Vulvovaginal candidiasis | S/E: vulvar/vaginal burning |
| danazol (Cyclomen® – CAN)  
(Danocrine® – US) | Synthetic steroid that inhibits pituitary gonadotropin output and ovarian steroid synthesis Has mild androgenic properties | 200-800 mg in 2-3 divided doses Used for 3-6 mo  
Biannual hepatic US required if >6 mo use | Endometriosis  
1° menorrhagia/DUB | S/E: weight gain, acne, mild hirsutism, hepatic dysfunction  
C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding, severely impaired renal/hepatic/cardiac function, porphyria, genital neoplasia, thromboembolic disease  
D/I: warfarin, carbamazepine, cyclosporine, tacrolimus, anti-hypertensives |

**GTN Diagnosis**
- β-hCG plateau: <10% drop in β-hCG over four values in 3 wk (e.g. days 1, 7, 14, and 21) OR
- β-hCG rise >20% in any two values over two wk or longer (e.g. measure at days 1, 7, 14) OR
- β-hCG persistently elevated >6 mo OR
- Metastases on workup
Table 30. Common Medications (continued)

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Action</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Side Effects (S/E), Contraindications (C/I), Drug Interactions (D/I)</th>
</tr>
</thead>
</table>
| doxycycline            | Tetracycline derivative; inhibit protein synthesis | 100 mg PO bid x 7 d | Chlamydia, gonococcal infection, syphilis | S/E: GI upset, hepatotoxicity
C/I: pregnancy, severe hepatic dysfunction
D/I: warfarin, digoxin |
| fluconazole (Diflucan®) | Antifungal; disrupt fungal cell membrane | 150 mg PO x 1 dose | Vulvovaginal candidiasis unresponsive to clotrimazole | S/E: headache, rash, N/V, abdominal pain, diarrhea
D/I: terfenadine, cisapride, astemizole, hydrochlorothiazide, phenytoin, warfarin, rifampin |
| leuprolide (Lupron®)   | Synthetic GnRH analog induces reversible hypoestrogenic state | 3.75 mg IM q1mo or 11.25 mg IM q3mo Usually ≤6 mg, check bone density if >6 mg. Retreatment with Lupron® alone not recommended because of effects on bone density | Endometriosis Leiomyomata DUB Precocious puberty | S/E: hot flashes, sweats, headache, vaginitis, reduction in bone density, acne, GI upset
C/I: pregnancy, undiagnosed vaginal bleeding, breastfeeding |
| menotropin (Pergonal®) | Human gonadotropin with FSH and LH effects; induce ovulation and stimulate ovarian follicle development | 75-150 U of FSH and LH IM OD x 7-12 d, then 10,000 U hCG one day after last dose | Infertility | S/E: bloating, irritation at injection site, abdominal/pelvic pain, headache, N/V, multiple pregnancy
C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, undiagnosed uterine bleeding |
| metronidazole (Flagyl®) | Bactericidal; forms toxic metabolites which damage bacterial DNA | 2 g PO x 1 dose or 500 mg PO bid x 7 d | Bacterial vaginosis, trichomonas vaginitis | S/E: headache, dizziness, N/V, diarrhea, disulfiram-like reaction (flushing, tachycardia, N/V)
C/I: pregnancy (1st trimester)
D/I: cisapride, warfarin, cimetidine, lithium, alcohol, amiodarone, milk thistle, carbamazepine |
| oxybutinin (Ditropan®) | Anticholinergic – relaxes bladder smooth muscle, inhibits involuntary detrusor contraction | 5 or 10 mg/d PO May increase doses by 5 mg weekly to a max of 30 mg/d | Overactive bladder (urge incontinence) | S/E: dry mouth/eyes, constipation, palpitations, urinary retention, dizziness, headache
C/I: glaucoma, GI ileus, severe colitis, obstructive uropathy, use with caution if impaired hepatic/renal function |
| tolterodine (Detrol®)  | Anticholinergic | 1-2 mg PO bid | Overactive bladder (urge incontinence) | S/E: anaphylaxis, psychosis, tachycardia, dry mouth/eyes, headache, constipation, urinary retention, chest pain, abdominal pain
C/I: glaucoma, gastric/urinary retention, use with caution if impaired hepatic/renal function |
| tranexamic acid (Cyklokapron®) | Anti-fibrinolytic, reversibly inhibits plasminogen activation | 1-1.5 g tid-qid for first 4 d of cycle Max 4 g/d Ophthalmic check if used for several wk | Menorrhagia | S/E: N/V, diarrhea, dizziness, rare cases of thrombosis, abdominal pain, MSK pain
C/I: thromboembolic disease, acquired disturbances of colour vision, subarachnoid hemorrhage, age < 15 yr |
| ulipristal acetate (Fibristol®) | Selective progesterone receptor modulator (SPRM) | 5 mg PO OD for max 3 mo; first tablet taken anytime during first 7 days of menstruation | Leiomyoma (pre-operative) | S/E: headache, hot flushes, constipation, vertigo, endometrial thickening
C/I: pregnancy, undiagnosed vaginal bleeding, any gynecomancer |
| urofollitropin (Metrodin®) | FSH | 75 U/d SC x 7-12 d | Ovulation induction in PCOS | S/E: ovarian enlargement or cysts, edema and pain at injection site, arterial thromboembolism, fever, abdominal pain, headache, multiple pregnancy
C/I: primary ovarian failure, intracranial lesion (e.g. pituitary tumour), uncontrolled thyroid/adrenal dysfunction, ovarian cyst (not PCOS), pregnancy, abnormal uterine bleeding |
| combined oral contraceptive pill (OCP) | Ovulatory suppression by inhibiting LH and FSH Decidualization of endometrium Thickening of cervical mucus to prevent sperm penetration | | Contraception Disorders of menstruation | See Tables 8-12 |
| intrauterine device (IUD) copper IUD (Nova-T®) progesterone-releasing IUD (Mirena®, Jaydess®) | Copper IUD: mild foreign body reaction in endometrium which is toxic to sperm and alters sperm motility Progesterone-releasing IUD: decidualization of endometrium and thickening of cervical mucus, may suppress ovulation | | Contraceptive effects last 5 yr Same as above | See Table 8-12 |
Hematology

Hematology

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Basics of Hematology

- over $10^{11}$ blood cells are produced daily
- sites of hematopoiesis in adults: pelvis, sternum, vertebral bodies
- lifespan of mature cells in blood
  - erythrocytes (120 d), neutrophils (~1 d), platelets (10 d), lymphocytes (varies – memory cells persist for years)
- role of lymphoid organs
  - thymus: site of T-cell maturation, involutes with age
  - lymph nodes: sites of B and T-cell activation (adaptive immune response)

Figure 1. Hematopoiesis
Complete Blood Count

Table 1. Common Terms Found on CBC

<table>
<thead>
<tr>
<th>Test</th>
<th>Definition</th>
<th>Normal Values*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Red Blood Cell (RBC) Count</td>
<td>The number of RBCs per volume of blood</td>
<td>4.2-6.9 x 10^6/mm³</td>
</tr>
<tr>
<td>Hemoglobin (Hb)</td>
<td>Amount of oxygen-carrying protein in the blood</td>
<td>130-180 g/L (male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>120-160 g/L (female)</td>
</tr>
<tr>
<td>Hematocrit (Hct)</td>
<td>Percentage of a given volume of whole blood occupied by packed RBCs</td>
<td>45%-62% (male)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>37%-48% (female)</td>
</tr>
<tr>
<td>Mean Corpuscular Volume (MCV)</td>
<td>Measurement of size of RBCs</td>
<td>80-100 µm³</td>
</tr>
<tr>
<td>Mean Corpuscular Hb (MCH)</td>
<td>Amount of oxygen-carrying Hb inside RBCs</td>
<td>27-32 pg/cell</td>
</tr>
<tr>
<td>Mean Corpuscular Hb Concentration (MCHC)</td>
<td>Average concentration of Hb inside RBCs</td>
<td>32%-36%</td>
</tr>
<tr>
<td>RBC Distribution Width (RDW)</td>
<td>Measurement of variance in RBC size</td>
<td>11.0%-15.0%</td>
</tr>
<tr>
<td>White Blood Cell (WBC) Count</td>
<td>The number of WBCs per volume of blood</td>
<td>4.3-10.8 x 10^9/mm³</td>
</tr>
<tr>
<td>WBC Differential</td>
<td>Neutrophils</td>
<td>1.8-7.8 x 10^9/mm³</td>
</tr>
<tr>
<td></td>
<td>Lymphocytes</td>
<td>0.7-4.5 x 10^9/mm³</td>
</tr>
<tr>
<td></td>
<td>Monocytes</td>
<td>0.1-1.0 x 10^9/mm³</td>
</tr>
<tr>
<td></td>
<td>Eosinophils</td>
<td>0.0-0.4 x 10^9/mm³</td>
</tr>
<tr>
<td></td>
<td>Basophils</td>
<td>0.0-0.2 x 10^9/mm³</td>
</tr>
<tr>
<td>Platelet Count</td>
<td>The number of platelets per volume of blood</td>
<td>150-400 x 10^9/mm³</td>
</tr>
<tr>
<td>Mean Platelet Volume (MPV)</td>
<td>Measurement of platelet size</td>
<td></td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>Immature RBCs that contain no nucleus but have residual RNA</td>
<td>Normally make up 1% of total RBC count</td>
</tr>
</tbody>
</table>

*Normal values may vary depending on site and age

Approach to Interpreting a CBC

1. consider values in the context of individual's baseline
   - up to 5% of population without disease may have values outside “normal” range
   - an individual may display a clinically significant change from their baseline without violating “normal” reference range
2. is one cell line affected or are several?
   - if all lines are low: pancytopenia (see Pancytopenia, H8)
   - if RBCs and platelets are low: consider a MAHA (see H22)
   - if single cell line affected: see Common Presenting Problems, H6

Blood Film Interpretation

RED BLOOD CELLS

Size
- microcytic (MCV <80), normocytic (MCV = 80-100), macrocytic (MCV >100)
- anisocytosis: RBCs with increased variability in size (increased RDW)
  - iron deficiency anemia, hemolytic anemias, myelofibrosis, blood transfusion, MDS

Colour
- hypochromic: increase in size of central pallor (normal = less than 1/3 of RBC diameter)
  - iron deficiency anemia, anemia of chronic disease, sideroblastic anemia
- polychromasia: increased reticulocytes (pinkish-blue cells)
  - increased RBC production by bone marrow

Shape
- poikilocytosis: increased proportion of RBCs of abnormal shape
  - iron deficiency anemia, myelofibrosis, severe B₁₂ deficiency, MDS, burns
Table 2. Common Erythrocyte Shapes

<table>
<thead>
<tr>
<th>Shape</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discocyte (Discocyte)</td>
<td>Biconcave disc</td>
<td>Normal RBC</td>
</tr>
<tr>
<td>Spherocyte</td>
<td>Spherical RBC (due to loss of membrane)</td>
<td>Hereditary spherocytosis, immune hemolytic anemia, post-transfusion</td>
</tr>
<tr>
<td>Elliptocyte/Ovalocyte</td>
<td>Oval-shaped, elongated RBCs</td>
<td>Hereditary elliptocytosis, megaloblastic anemia, iron-deficiency, MDS (myelodysplastic syndrome)</td>
</tr>
<tr>
<td>Schistocyte (Helmet cell)</td>
<td>Fragmented cells (due to traumatic disruption of membrane)</td>
<td>Microangiopathic hemolytic anemia (HUS/ TTP, DIC, preeclampsia, HELLP, malignant HTN, vasculitis, glomerulonephritis, prosthetic heart valve</td>
</tr>
<tr>
<td>Sickle Cell</td>
<td>Sickle-shaped RBC (due to polymerization of hemoglobin S)</td>
<td>Sickle cell disorders: HbSC, HbSS</td>
</tr>
<tr>
<td>Codocyte (Target cell)</td>
<td>&quot;Bull's eye&quot; on dried film</td>
<td>Liver disease, hemoglobin SC, thalassemia, Fe deficiency, asplenia</td>
</tr>
<tr>
<td>Dacrocyte (Teardrop cell)</td>
<td>Single pointed end, looks like a teardrop</td>
<td>Myelofibrosis, thalassemia major, megaloblastic anemia, bone marrow infiltration</td>
</tr>
<tr>
<td>Acanthocyte (Spur cell)</td>
<td>Distorted RBC with irregularly distributed thorn-like projections (due to abnormal membrane lipids)</td>
<td>Severe liver disease (spur cell anemia), starvation/anorexia, post-splenectomy</td>
</tr>
<tr>
<td>Echinocyte (Burr cell)</td>
<td>RBC with numerous regularly spaced, small spiny projections</td>
<td>Uremia, HUS, bums, cardiopulmonary bypass, post-transfusion, storage artifact</td>
</tr>
<tr>
<td>Rouleaux Formation</td>
<td>Aggregates of RBC resembling stacks of coins (due to increased plasma concentration of high molecular weight proteins)</td>
<td>Pregnancy is most common cause (due to physiological increase in fibrinogen) inflammatory conditions (due to polyclonal immunoglobulins) Plasma cell dyscrasias (due to monoclonal paraproteinemia, e.g. multiple myeloma, macroglobulinemia) Storage artifact</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, and low platelet count; HUS = hemolytic uremic syndrome; TTP = thrombotic thrombocytopenic purpura
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

Table 3. RBC Inclusions

<table>
<thead>
<tr>
<th>Inclusions</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleus</td>
<td>Present in erythroblasts (immature RBCs)</td>
<td>Hyperplastic erythropoiesis (seen in hypoxia, hemolytic anemia), BM infiltration disorders, MPNs (MF)</td>
</tr>
<tr>
<td>Heinz bodies</td>
<td>Denatured and precipitated hemoglobin</td>
<td>G6PD deficiency (post-exposure to oxidant), thalassemia, unstable hemoglobins</td>
</tr>
<tr>
<td>Howell-Jolly Bodies</td>
<td>Small nuclear remnant resembling a pyknotic nucleus</td>
<td>Post-splenectomy, hyposplenism (sickle cell disease), neonates, megaloblastic anemia</td>
</tr>
<tr>
<td>Basophilic Stippling</td>
<td>Deep blue granulations indicating ribosome aggregation</td>
<td>Thalassemia, heavy metal (Pb, Zn, Ag, Hg) poisoning, megaloblastic anemia, hereditary (pyrimidine 5'nucleotidase deficiency)</td>
</tr>
<tr>
<td>Sideroblasts</td>
<td>Erythrocytes with Fe containing granules in the cytoplasm</td>
<td>Hereditary, idiopathic, drugs, hypothyroidism (see Sideroblastic Anemia, H16), myelodysplastic syndrome, toxins (lead)</td>
</tr>
</tbody>
</table>

BM = bone marrow; MF = myelofibrosis; MPN = myeloproliferative neoplasm
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012
WHITE BLOOD CELLS
• lymphocytes: comprise 30-40% of WBCs; great variation in “normal” lymphocyte morphology
• neutrophils
  ▪ normally only mature neutrophils (with 3-4 lobed nucleus) and band neutrophils (immediate precursor with horseshoe-shaped nucleus) are found in circulation
  ▪ hypersegmented neutrophil: >5 lobes suggests megaloblastic process (B12 or folate deficiency)
  ▪ left shift (increased granulocyte precursors)
    ▪ seen in leukemoid reactions: acute infections, pregnancy, neonates, hypoxia, shock, myeloproliferative neoplasms (CML, MF)
• blasts
  ▪ immature, undifferentiated precursors; associated with acute leukemia, MDS, G-CSF (growth factor that stimulates neutrophil production) use

<table>
<thead>
<tr>
<th>Appearance</th>
<th>Definition</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reed-Sternberg Cell</td>
<td>Giant, multinucleated B-lymphocyte, only seen with bone marrow specimens (classic ‘owl-eye’ morphology)</td>
<td>Primarily Hodgkin lymphoma, also seen in some non-Hodgkin lymphoma, CLL, and EBV infection</td>
</tr>
<tr>
<td>Smudge Cell</td>
<td>Lymphocytes damaged during blood film preparation indicating cell fragility</td>
<td>CLL and other lymphoproliferative disorders Pathognomonic in EBV infection</td>
</tr>
<tr>
<td>Auer Rod</td>
<td>Clumps of granular material that form long needles in the cytoplasm of myeloblasts</td>
<td>Pathognomonic for acute myeloid leukemia (AML)</td>
</tr>
<tr>
<td>Atypical Lymphocyte</td>
<td>Pale blue cytoplasm following RBC edges with pink granules</td>
<td>Viruses (particularly EBV) T-cell large granular lymphocyte leukemia (T-LGL)</td>
</tr>
</tbody>
</table>

EBV = Epstein-Barr virus, CLL = chronic lymphocytic leukemia
Illustrations: Ayalah Hutchins and Merry Shiyu Wang 2012

PLATELETS
• small, purple, anuclear cell fragments

Bone Marrow Aspiration and Biopsy

• sites: posterior iliac crest, sternum
• analyses: most often done together
  ▪ aspiration: takes a fluid marrow sample for cellular morphology, flow cytometry, cytogenticis, molecular studies, microbiology (C&S, acid-fast bacilli, PCR)
  ▪ note: differential diagnosis for a “dry tap”: MF, hairy cell leukemia, bone marrow infiltration
  ▪ biopsy: takes a sample of intact bone marrow to assess histology and immunohistochemistry

Indications
• unexplained CBC abnormalities
• diagnosis and evaluation of infiltrating cancers: plasma cell disorders, leukemias, solid tumours
• diagnosis and staging of lymphoma or solid tumours
• evaluate iron metabolism and stores (gold standard, but rarely done)
• evaluate suspected deposition and storage disease (e.g. amyloidosis, Gaucher’s disease)
• evaluate fever of unknown origin, suspected mycobacterial, fungal/parasitic infections, or granulomatous disease
• evaluate unexplained splenomegaly
• confirm normal bone marrow in potential allogenic hematopoietic cell donor

Contraindications
• absolute: untreated hemophilia, severe DIC, infection over skin site
• relative: recent warfarin use with INR >2.0, liver disease with associated coagulopathy
• thrombocytopenia is not a contraindication; may need platelet transfusion prior to procedure
Common Presenting Problems

Anemia

Definition
- a decrease in red blood cell (RBC) mass that can be detected by hemoglobin (Hb) concentration, hematocrit (Hct), and RBC count
  - adult males: Hb < 130 g/L or Hct < 0.41
  - adult females: Hb < 120 g/L or Hct < 0.36 (changes with pregnancy and trimester)

Clinical Features
- history
  - symptoms of anemia (order of onset): fatigue, headache, light-headedness, malaise, weakness, decreased exercise tolerance, dyspnea, palpitations, dizziness, tinnitus, syncope
  - acute vs. chronic, bleeding, systemic illness, diet (Fe, B12 sources), alcohol, family history
  - menstrual history: menorrhagia, menometrorrhagia
  - rule out pancytopenia (recurrent infection, mucosal bleeding, easy bruising)
- physical signs
  - HEENT: pallor in mucous membranes and conjunctiva at Hb < 90 g/L (< 9 g/dL), ocular bruits at Hb < 55 g/L (< 5.5 g/dL), angular chelosis, jaundice
  - cardiac: tachycardia, orthostatic hypotension, systolic flow murmur, wide pulse pressure, signs of CHF
  - dermatologic: pallor in palmar skin creases at Hb < 75 g/L, jaundice (if due to hemolysis), nail changes, glossitis

Investigations
- rule out dilutional anemia (low Hb due to increased effective circulating volume)
- CBC with differential (MCV, RDW, RBC count)
- reticulocyte count - very useful to evaluate for blood cell production problems
- blood film
- rule out nutritional deficit, gastrointestinal and genitourinary disease in iron deficiency anemia
- additional laboratory investigations as indicated (see Microcytic Anemia, H13, Normocytic Anemia, H17, Hemolytic Anemia, H18, and Macrocytic Anemia, H24)

Erythrocytosis

Definition
- an increase in the number of RBCs: Hb > 185 g/L or Hct > 52% (males); Hb > 165 or Hct > 47% (females and African males)

Etiology
- relative/spurious erythrocytosis (decreased plasma volume): diuretics, severe dehydration, burns, “stress” (Gaissböck’s syndrome)
- absolute erythrocytosis
Table 5. Etiology of Erythrocytosis

<table>
<thead>
<tr>
<th>Primary</th>
<th>Secondary</th>
<th>Inappropriate Production of Erythropoietin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycythemia Vera (PV)</td>
<td>Physiologic (poor tissue oxygenation/hypoxia)</td>
<td>Tumours</td>
</tr>
<tr>
<td>(see Polycythemia Vera, H41)</td>
<td>Carbon monoxide poisoning</td>
<td>Hepatocellular carcinoma</td>
</tr>
<tr>
<td></td>
<td>Heavy smoking</td>
<td>Renal cell carcinoma</td>
</tr>
<tr>
<td></td>
<td>High altitude</td>
<td>Cerebellar hemangioblastoma</td>
</tr>
<tr>
<td>Pulmonary Disease</td>
<td>COPD</td>
<td>Pheochromocytoma</td>
</tr>
<tr>
<td></td>
<td>Sleep apnea</td>
<td>Uterine leiomyoma</td>
</tr>
<tr>
<td></td>
<td>Pulmonary hypertension</td>
<td>Ovarian tumour</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>R to L shunt (Eisenmenger syndrome)</td>
<td>Other</td>
</tr>
<tr>
<td></td>
<td>RBC defects (Hb with increased O₂ affinity, methemoglobinemia)</td>
<td>Polycystic kidney disease</td>
</tr>
</tbody>
</table>

Clinical Features
- secondary to high red cell mass and hyperviscosity
  - headache, dizziness, tinnitus, visual disturbances, hypertensive symptoms
  - symptoms of angina, congestive heart failure, aquagenic pruritus
- thrombosis (venous or arterial) or bleeding (abnormal platelet function)
- physical findings
  - splenomegaly ± hepatomegaly, facial plethora/ruddy complexion (70%) and/or palms, gout

Investigations
- serum erythropoietin (EPO): differentiates primary (low/normal) from other etiologies (elevated)
- search for tumour as source of EPO as indicated (e.g. abdominal U/S, CT head)
- JAK-2 mutation analysis: positive in >96% of cases of PV
  - only send if low/normal EPO level
- ferritin (iron deficiency can mask the diagnosis)

Treatment
- if primary: see Polycythemia Vera, H41
- if secondary: treat underlying cause
  - O₂ for hypoxemia, CPAP for sleep apnea, surgery for EPO-secreting tumours
  - often cardiologists will be hesitant to treat high Hct in cyanotic patients

Thrombocytopenia

Definition
- platelet count <150 x10⁹/L

Clinical Features
- history: bleeding gums, epistaxis, bleeding post-surgical procedures, metromenorrhagia
- physical exam: bruising, petechiae, ecchymoses, non-palpable purpura
- hemarthrosis and deep muscle hematomas are rarely initial signs in patients with primary hemostatic disorders
- see Disorders of Primary Hemostasis, H27 for complications

Investigations
- CBC and differential
- blood film
  - decreased production: other cell line abnormalities, blasts, hypersegmented PMNs, leukoerythroblastic changes
  - increased destruction: large platelets, schistocytes (seen in MAHA)
  - rule out platelet clumping
- workup for nutritional deficiencies: B₁₂, RBC folate
- PT/INR, aPTT and fibrinogen if DIC suspected
- LFTs

Rule-of-thumb: a deficit in all cell lines suggests decreased production, sequestration, or hemodilution, a deficit in platelets and RBCs suggests non-immune destruction, and an isolated thrombocytopenia suggests an immune-mediated destruction

Must rule out factitious thrombocytopenia: platelet clumping (secondary to EDTA antibodies from collection tube). This can be seen on blood film and confirmed by repeating in a citrated sample (i.e. using a sodium citrate tube to collect blood, rather than EDTA)

In hospitalized patients, drugs and infection account for the majority of cases of thrombocytopenia

Treatments
- life threatening bleeding: platelet transfusion (repeat CBC 1 h post-transfusion to confirm an appropriate rise in counts)
- if secondary: treat underlying cause
- ITP: see Immune Thrombocytopenic Purpura, H27
**Thrombocytosis**

**Definition**
- platelet count >400 x10^9/L
- primary thrombocytosis (uncommon): due to myeloproliferative neoplasms (e.g. CML, polycythemia vera, primary myelofibrosis, essential thrombocytosis; rarely associated with MDS)
- reactive/secondary thrombocytosis (common): acute phase reactant (e.g. surgery, inflammation, infection, trauma, bleeding, iron deficiency, neoplasms, ischemic injury)

**Clinical Features**
- history: trauma, surgery, splenectomy, infection, inflammation, bleeding, iron deficiency, prior diagnosis of chronic hematologic disorder, constitutional symptoms (malignancy)
- vasomotor symptoms: headache, visual disturbances, lightheadedness, atypical chest pain, acral dysesthesia, erythromelalgia, livedo reticularis, aquagenic pruritus
- clotting risk, bleeding risk (rare)
- physical exam: splenomegaly can be seen in myeloproliferative neoplasms (MPNs)

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MPN/MDS

**Treatment**
- primary: ASA ± cytoreductive agents (e.g. hydroxyurea, anagrelide, interferon-α)
- secondary: treat underlying cause

**Pancytopenia**

**Definition**
- a decrease in all hematopoietic cell lines

**Clinical Features**
- anemia: fatigue (see Anemia, H6)
- leukopenia: recurrent infections (see Neutropenia, H9)
- thrombocytopenia: mucosal bleeding (see Thrombocytopenia, H7)

**Investigations**
- CBC, peripheral blood film, serum ferritin concentration, B12, RBC folate
- non-specific markers of infection or inflammation (e.g. CRP, ESR, ferritin)
  - work up as per Figure 4 and presenting symptoms/physical exam
- if reactive process has been ruled out, bone marrow biopsy may be required to rule out MDS
Neutrophilia

Definition
• variable definition, but generally an absolute neutrophil count (ANC) >7.7 x 10^9/L (WHO definition)

Etiology
• primary neutrophilia
  ▪ chronic myeloid leukemia (CML)
  ▪ other myeloproliferative disorders: PV, ET, myelofibrosis
  ▪ hereditary neutrophilia (autosomal dominant)
  ▪ chronic idiopathic neutrophilia in otherwise healthy patients
  ▪ leukocyte adhesion deficiency
• secondary neutrophilia
  ▪ stress/exercise/epinephrine: movement of neutrophils from marginated pool into circulating pool
  ▪ obesity
  ▪ infection: leukocytosis with left shift ± toxic granulation, Döhle bodies (intra-cytoplasmic structures composed of agglutinated ribosomes)
  ▪ inflammation: e.g. rheumatoid arthritis (RA), IBD, chronic hepatitis, MI, PE, burns
  ▪ malignancy: hematologic (i.e. marrow invasion by tumour) and non-hematologic (especially large cell lung cancer)
  ▪ medications: glucocorticoids, β-agonists, lithium, G-CSF

Clinical Features
• look for signs and symptoms of fever, inflammation, malignancy to determine appropriate further investigations
  ▪ including lymph nodes and organomegaly
• examine oral cavity, teeth, peri-rectal area, genitals, and skin for signs of infection

Investigations
• CBC and differential: mature neutrophils or bands >20% of total WBC suggests infection/inflammation
• blood film: Döhle bodies, toxic granulation, cytoplasmic vacuoles in infection
• may require bone marrow biopsy if MPN suspected

Treatment
• directed at underlying cause

Neutropenia

Definition
• mild: ANC 1.0-1.5 x 10^9/L
• moderate: ANC 0.5-1.0 x 10^9/L (risk of infection starts to increase)
• severe: ANC <0.5 x 10^9/L
• profound: ANC <0.1 x 10^9/L for >7 d
Etiology

Table 6. Etiology of Neutropenia

<table>
<thead>
<tr>
<th>Decreased Production</th>
<th>Peripheral Destruction/Sequestration</th>
<th>Excessive Margination (Transient Neutropenia)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>Anti-neutrophil antibodies</td>
<td>Idiopathic (most common)</td>
</tr>
<tr>
<td>Viral hepatitis, EBV, HIV, TB, typhoid, malaria</td>
<td>Spleen or lung trapping</td>
<td>Overwhelming bacterial infection Hemodialysis</td>
</tr>
<tr>
<td>Hematological Diseases</td>
<td>Autoimmune disorders: RA (Felty’s syndrome), SLE Granulomatosis with polyangitis (formerly Wegener’s)</td>
<td>Racial variation (e.g. African or Ashkenazi Jewish descent)</td>
</tr>
<tr>
<td>Drug-Induced</td>
<td>Drugs: haptens (e.g. α-methyldopa)</td>
<td></td>
</tr>
<tr>
<td>Alkylating agents, antimetabolites, anticonvulsants, antipsychotics, anti-inflammatory agents, anti-thyroid drugs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxins/Chemicals</td>
<td>High dose radiation, benzene, DDT</td>
<td></td>
</tr>
<tr>
<td>Nutritional Deficiency</td>
<td>B12, folate</td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>Constitutional neutropenia, benign cyclic neutropenia, cyclical</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- fever, chills (only if infection present)
- infection by endogenous bacteria (e.g. S. aureus, gram negatives from GI and GU tract)
- painful ulceration on skin, anus, mouth, and throat following colonization by opportunistic organisms
- avoid digital rectal exam

Investigations
- dependent on degree of neutropenia, history, and symptoms
- ranges from observation with frequent CBCs to bone marrow aspiration and biopsy

Treatment
- regular dental care: chronic gingivitis and recurrent stomatitis major sources of morbidity
- treatment of febrile neutropenia (see Infectious Diseases, ID45)
- in severe immune-mediated neutropenia, G-CSF may increase neutrophil counts
  - if no response to G-CSF, consider immunosuppression (e.g. steroids, cyclosporine, methotrexate)

Lymphocytosis

Definition
- absolute lymphocyte count >4 x 10^9/L

Etiology
- infection
  - viral infections (majority); particularly mononucleosis
  - TB, pertussis, brucellosis, toxoplasmosis
  - smoking
  - physiologic response to stress (e.g. trauma, status epilepticus)
  - hypersensitivity (e.g. drugs, serum sickness)
  - autoimmune (e.g. rheumatoid arthritis)
  - neoplasm (e.g. ALL, CLL, lymphoma)

Investigations
- peripheral smear

Treatment
- treat underlying cause

Lymphopenia

Definition
- absolute lymphocyte count <1.5 x 10^9/L

Etiology
- idiopathic CD4+ lymphocytopenia
- radiation
- HIV/AIDS, hepatitis B, hepatitis C
- malignancy/chemotherapeutic agents
- malnutrition, alcoholism
- autoimmune disease (e.g. SLE)
Clinical Features
- opportunistic infections (see Infectious Diseases, ID30, ID34)

Treatment
- treat underlying cause
- treat opportunistic infections aggressively and consider antimicrobial prophylaxis (see Infectious Diseases, ID30)

Eosinophilia

Definition
- absolute eosinophil count >0.5 x 10^9/L

Etiology
- primary: due to clonal bone marrow disorder
  - if no primary etiology identified, classified as hypereosinophilic syndrome
  - 6 mo of eosinophilia with no other detectable causes
- secondary
  - most common causes are parasitic (usually helminth) infections and allergic reactions
  - less common causes
    - polyarteritis nodosa, see Rheumatology, RH19
    - respiratory causes (asthma, eosinophilic pneumonia, Churg-Strauss)
    - cholesterol emboli
    - hematologic malignancy: see Chronic Myeloid Leukemia, H40 and Hodgkin Lymphoma, H45
    - adrenal insufficiency, see Endocrinology, E34
    - medications (penicillins)
    - atopic dermatitis

Treatment
- treat underlying cause
- ensure strongyloides serology is collected to rule out infection before initiating steroids for patients at risk

Agranulocytosis

Definition
- severe depletion of granulocytes (neutrophils, eosinophils, basophils) from the blood and granulocyte precursors from bone marrow

Etiology
- associated with medications in 70% of cases: e.g. chemotherapy, clozapine, thionamides (antithyroid drugs), sulfasalazine, and ticlopidine
  - immune-mediated destruction of circulating granulocytes by drug-induced antibodies or direct toxic effects upon marrow granulocytic precursors

Clinical Features
- abrupt onset of fever, chills, weakness, and oropharyngeal ulcers

Prognosis
- high fatality without vigorous treatment

Investigations/Treatment
- discontinue offending drug
- pan-culture and screen for infection if patient is febrile (blood cultures x2, urine culture, and chest x-ray as minimum, initiate broad-spectrum antibiotics)
- consider bone marrow aspirate and biopsy if cause unclear
- consider G-CSF

Leukemoid Reactions

- blood findings resembling those seen in certain types of leukemia which reflect the response of healthy BM to cytokines released due to infection or trauma
- leukocytosis >50 x 10^9/L, marked left shift (myelocytes, metamyelocytes, bands in peripheral blood smear)
Etiology
• important to rule out CML
• differential diagnosis
  ▪ myeloid progenitors: pneumonia, other acute bacterial infections, intoxications, burns, malignant disease, severe hemorrhage or hemolysis
  ▪ lymphoid progenitors: pertussis, TB, infectious mononucleosis
  ▪ monocytic progenitors: TB

Approach to Lymphadenopathy

History
• constitutional/B-symptoms: seen in TB, lymphoma, other malignancies
• growth pattern: acute vs. chronic
• exposures: cats (cat scratch – Bartonella henselae), ticks (Lyme disease – Borrelia burgdorferi), high risk behaviors (HIV)
• joint pain/swelling, rashes (connective tissue disorder)
• pruritus (seen in Hodgkin lymphoma)
• medications (can cause serum sickness → lymphadenopathy)

Physical Exam
• basic assessment: occipital, preauricular, submandibular, cervical, supra-/infra-clavicular, axillary, epitrochlear, inguinal, popliteal nodes
  ▪ characteristics of lymph nodes: location, size, tenderness, consistency, mobility, borders, contour
  ▪ look for signs of infection in regions which lymph nodes drain
• determine if lymphadenopathy is localized or generalized
• localized: typically reactive or neoplastic
  ▪ right (mediastinal, bronchogenic, esophageal cancer)
  ▪ left (gastric, gall bladder, pancreas, renal, testicular/ovarian cancer)
• axillary (cat scratch fever, breast cancer, metastatic cancer)
• epitrochlear (infections, sarcoidosis, lymphoma)
• lower/inguinal (STDs, skin, cervix, vulva/genital cancer)
• generalized: see Table 8
• thorough examination required to assess for systemic disease

Investigations
• CBC and differential, blood film
• ± tuberculin test, HIV RNA, VDRL, Monospot*/EBV serology, ANA, imaging as indicated
• if localized and no symptoms suggestive of malignancy, can observe 3-4 wk (if no resolution → biopsy)
• excisional biopsy is preferred as it preserves node architecture (essential for diagnosing lymphoma)
• in areas difficult to access (retroperitoneal, mediastinal/hilar) multiple core biopsies may be more practical/feasible
• FNA should NOT be used for diagnostic purposes in lymphoproliferative disease (use excisional biopsy instead)
  ▪ helpful for recurrence of solid tumour malignancy

Table 7. Inflammatory vs. Neoplastic Lymph Nodes

<table>
<thead>
<tr>
<th>Feature</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consistency</td>
<td>Rubbery</td>
<td>Firm/hard</td>
</tr>
<tr>
<td>Mobility</td>
<td>Mobile</td>
<td>Matted/immobile</td>
</tr>
<tr>
<td>Tenderness</td>
<td>Tender</td>
<td>Non-tender</td>
</tr>
<tr>
<td>Size</td>
<td>&lt;2 cm</td>
<td>&gt;2 cm</td>
</tr>
</tbody>
</table>

*Note: these classifications are not absolute; lymphoma and CLL nodes can feel rubbery and are frequently mobile, non-tender

Table 8. Differential Diagnosis of Generalized Lymphadenopathy

<table>
<thead>
<tr>
<th>Reactive</th>
<th>Inflammatory</th>
<th>Neoplastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacterial (TB, Lyme, brucellosis, cat scratch disease, syphilis)</td>
<td>Collagen disease (RA, dermatomyositis, SLE, vasculitis, Sjögren’s)</td>
<td>Lymphoproliferative disorder/lymphoma</td>
</tr>
<tr>
<td>Viral (EBV, CMV, HIV)</td>
<td>Drug hypersensitivity</td>
<td>Metastatic cancer</td>
</tr>
<tr>
<td>Parasitic (toxoplasmosis)</td>
<td>Sarcoidosis, amyloidosis</td>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Fungal (histoplasmosis)</td>
<td>Serum sickness</td>
<td></td>
</tr>
</tbody>
</table>

Constitutional/B-Symptoms
• Unexplained temperature >38°C
• Unexplained weight loss (>10% of body weight in 6 mo)
• Night sweats

Drugs that can cause Lymphadenopathy
• Allopurinol
• Atenolol
• Captopril
• Carbamazepine
• Cephalosporins
• Gold
• Hydralazine
• Penicillin
• Phenytoin
• Primidone
• Pyrimethamine
• Quinidine
• Sulfonamides
**Approach to Splenomegaly**

Table 9. Differential Diagnosis of Splenomegaly

<table>
<thead>
<tr>
<th>Category</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased Demand for Splenic Function</td>
<td>Infectious: CMV, Bacterial endocarditis</td>
</tr>
<tr>
<td>Hematological</td>
<td>Hemoglobinopathies</td>
</tr>
<tr>
<td>Spherocytosis</td>
<td>Hemolytic</td>
</tr>
<tr>
<td>Sequestration crisis</td>
<td>Nutritional anemias</td>
</tr>
<tr>
<td>Nutritional anemias</td>
<td>Elliptocytosis</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Infectious: Felty syndrome, Still’s disease</td>
</tr>
<tr>
<td>Hematological</td>
<td>SLE</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Sarcoidosis</td>
</tr>
<tr>
<td>Infiltrative</td>
<td>Non-Malignant: Benign metaplasia, Amyloidosis</td>
</tr>
<tr>
<td></td>
<td>Lysosomal storage diseases</td>
</tr>
<tr>
<td></td>
<td>Leukemia (CML, CLL)</td>
</tr>
<tr>
<td></td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td></td>
<td>Metastatic tumour</td>
</tr>
</tbody>
</table>

The underlined conditions cause massive splenomegaly (spleen crosses midline or reaches pelvis)

**History**
- constitutional symptoms, feeling of fullness in LUQ
- signs or symptoms of infectious disease
- history of liver disease, hemolytic anemia, or high-risk exposures

**Physical Exam**
- jaundice, petechiae
- signs of chronic liver disease
- percussion (Castell’s sign, Traube’s space, Nixon’s method) and palpation
- associated lymphadenopathy or hepatomegaly
- signs of CHF

**Investigations**
- CBC and differential, blood film
- as indicated: liver enzymes/liver function tests, reticulocyte count, Monospot®/EBV, haptoglobin, LDH, infectious, and autoimmune workup
- imaging
  - ultrasound of abdomen/liver to rule out cirrhosis and portal vein thrombosis
  - echo for cardiac function
  - CT to rule out lymphoma

**Microcytic Anemia**
- MCV <80 fL
- see Figure 2, *Approach to Anemia*, H6

Table 10. Iron Indices and Blood Film in Microcytic Anemia

<table>
<thead>
<tr>
<th>Lab Tests</th>
<th>Blood Film</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferritin</td>
<td>Hypochromic, microcytic</td>
</tr>
<tr>
<td>Serum Iron</td>
<td></td>
</tr>
<tr>
<td>TIBC</td>
<td></td>
</tr>
<tr>
<td>RDW</td>
<td></td>
</tr>
</tbody>
</table>

**Iron Metabolism**

**Iron Intake (Dietary)**
- average North American adult diet = 10-20 mg iron (Fe) daily
- absorption is 5-10% (0.5-2 mg/d); enhanced by citric acid, ascorbic acid (vitamin C) and reduced by polyphenols (e.g. in tea), phytate (e.g. in bran), dietary calcium, and soy protein
- males have positive Fe balance; up to 20% of menstruating females have negative Fe balance
Iron Absorption and Transport
- dietary iron is absorbed in the duodenum (impaired by IBD, celiac disease, etc.)
- in circulation the majority of non-heme iron is bound to transferrin which transfers iron from enterocytes and storage pool sites (macrophages of the reticuloendothelial system and hepatocytes) to RBC precursors in the bone marrow

Iron Levels
- hepcidin is a hormone produced by hepatocytes that regulates systemic iron levels
  - binds to iron exporter ferroportin (on duodenal enterocytes and reticuloendothelial cells) and induces its degradation, thereby inhibiting iron export into circulation
  - hepcidin production is increased in states of inflammation (thereby mediating anemia of chronic disease) or iron overload, and decreased in states where erythropoiesis is increased (e.g. hemolysis) or oxygen tension is low

Iron Storage
- ferritin
  - ferric iron (Fe³⁺) complexed to a protein called apoferritin (hepatocytes are main ferritin storage site)
  - small quantities are present in plasma in equilibrium with intracellular ferritin
  - also an acute phase reactant – can be spuriously elevated despite low Fe stores in response to a stressor
- hemosiderin
  - aggregates or crystals of ferritin with the apoferritin partially removed
  - macrophage-monocyte system is main source of hemosiderin storage

Iron Indices
- bone marrow aspirate: gold standard test for iron stores (rarely done)
- serum ferritin: most important blood test for iron stores
  - decreased in iron deficiency anemia
  - elevated in infection, inflammation, malignancy, liver disease, hyperthyroidism, and iron overload
- serum iron: measure of all non-heme iron present in blood
  - varies significantly daily
  - virtually all serum iron is bound to transferrin, only a trace is free or complexed in ferritin
- total iron binding capacity (TIBC): total amount of transferrin present in blood
  - normally, one third of TIBC is saturated with iron
  - high specificity for decreased iron, low sensitivity
- saturation
  - serum Fe divided by TIBC, expressed as a proportion or a percentage
  - low in iron deficiency anemia
- soluble transferrin receptor (sTfR)
  - reflects the availability of iron at the tissue level
  - the transferrin receptor is expressed on the surface of erythroblasts and is responsible for iron uptake – some is cleaved off and is present in circulation as sTfR

Figure 5. Iron metabolism
in iron deficient states more transferrin receptor is expressed on erythroblasts leading to an increase in sTfR
- low in reduced erythropoiesis and iron overload
- useful in determining iron deficiency in the setting of chronic inflammatory disorders (see Iron Deficiency Anemia)

## Iron Deficiency Anemia

- see Pediatrics, P47
- most common cause of anemia in North America

### Etiology
- increased demand
  - increased physiological need for iron in the body (e.g. pregnancy)
- decreased supply: dietary deficiencies (rarely the only etiology)
  - cow's milk (infant diet)
  - "tea and toast" diet (elderly)
  - absorption imbalances
  - post-gastrectomy
  - malabsorption (IBD of duodenum, celiac disease, autoimmune atrophic gastritis)
- increased losses
  - hemorrhage
    - obvious causes: menorrhagia, abnormal uterine bleeding, frank GI bleed
    - occult: peptic ulcer disease, GI cancer
  - hemolysis
    - intravascular (e.g. PNH, cardiac valve RBC fragmentation)
    - extravascular (e.g. immune hemolytic anemias)

### Clinical Features
- iron deficiency may cause fatigue before clinical anemia develops
- signs/symptoms of anemia: see Anemia, H6
- brittle hair, nail changes (brittle, koilonychia)
- Plummer-Vinson syndrome: dysphagia (esophageal webs), glossitis, angular stomatitis (inflammation and fissuring at the corners of the mouth)
- pica (appetite for non-food substances e.g. ice, paint, dirt)

### Investigations
- iron indices, including soluble transferrin receptor
  - low ferritin (<45 µg/L) is diagnostic of iron deficiency
  - ferritin is an acute phase reactant and is elevated in the setting of inflammatory conditions and liver disease; serum ferritin <100 µg/L in these settings is suggestive of iron deficiency, necessitating further workup
- peripheral blood film
  - hypochromic microcytosis: RBCs have low Hb levels due to lack of iron
  - pencil forms, anisocytosis
  - target cells (thin)
- bone marrow (gold standard but rarely done)
  - iron stain (Prussian blue) shows decreased iron in macrophages and in erythroid precursors (sideroblasts)
  - intermediate and late erythroblasts show micronormoblastic maturation

Iron deficiency anemia is a common presentation of chronic lower GI bleeds (right-sided colorectal cancer, angiodysplasia, etc.)
In males and in post-menopausal women, a GI workup is always warranted

Plummer-Vinson Syndrome Triad
- Dysphagia (esophageal)
- Glossitis
- Iron deficiency anemia

![Figure 6. Approach to interpreting iron indices](image-url)
**Treatment**
- treat underlying cause
- supplementation
  - oral (tablets, syrup)
    - ferrous sulphate 325 mg tid, ferrous gluconate 300 mg tid, or ferrous fumarate 300 mg tid
    - supplement until anemia corrects, then continue for 3+ mo until serum ferritin returns to normal
    - oral iron should be taken with citrus juice (vitamin C) to enhance absorption
  - IV (iron sucrose or dextran) can be used if patient cannot tolerate or absorb oral iron
- monitoring response
  - reticulocyte count will begin to increase after one wk
  - Hb normalizes by 10 g/L per wk (if no blood loss)
  - iron supplementation required for 4-6 mo to replenish stores

**Anemia of Chronic Disease**

**Etiology**
- infection, malignancy, inflammatory and rheumatologic disease, chronic renal and liver disease, endocrine disorders (e.g. DM, hypothyroidism, hypogonadism, hypopituitarism)

**Pathophysiology**
- an anemia of underproduction due to impaired iron utilization (hepcidin is a key regulatory peptide)
  - hepatic hepcidin production is increased in inflammatory processes, trapping iron in enterocytes and macrophages (via ferroportin inhibition) (see Figure 5)
  - reduced plasma iron levels make iron relatively unavailable for new hemoglobin synthesis
  - marrow unresponsive to normal or slightly elevated EPO
- mild hemolytic component is often present
- RBC survival is modestly decreased

**Investigations**
- diagnosis of exclusion
- associated with elevation in acute phase reactants (ESR, CRP, fibrinogen, platelets)
- peripheral blood
  - mild: usually normocytic and normochromic
  - moderate: may be microcytic and normochromic
  - severe: may be microcytic and hypochromic
  - absolute reticulocyte count is frequently low, reflecting overall decrease in RBC production
  - “classic” serum iron indices
    - serum iron and TIBC low, % saturation normal
    - serum ferritin is normal or increased
  - bone marrow
    - normal or increased iron stores
    - decreased or absent staining for iron in erythroid precursors

**Treatment**
- treat underlying disease
- only treat anemia in patients who can benefit from a higher hemoglobin
- IV iron if no benefit form PO iron (overcomes sequestration in enterocytes)
- erythropoietin indicated in chronic renal failure; not to be used if patient has concomitant curative solid tumour malignancy; ensure Hb target <110 g/L

**Sideroblastic Anemia**
- uncommon compared to iron deficiency anemia or anemia of chronic disease

**Sideroblasts**
- erythrocytes with iron-containing (basophilic) granules in the cytoplasm
  - “normal”: granules are small, randomly spread in the cytoplasm
  - found in healthy individuals
  - “ring”: iron deposits in mitochondria, forming a ring around the nucleus
  - abnormal, large granules
  - the hallmark of sideroblastic anemia

**Etiology**
- due to defects in heme biosynthesis in erythroid precursors
- hereditary (rare): X-linked; median survival 10 yr
- idiopathic (acquired)
  - refractory anemia with ringed sideroblasts: a subtype of MDS (see *Myelodysplastic Syndromes*, H39)
  - may be a preleukemic phenomenon (10% transform to AML)
  - reversible
    - drugs (isoniazid, chloramphenicol), alcohol, lead, copper deficiency, zinc toxicity, hypothyroidism

Iron-deficiency anemia commonly co-exists with anemia of chronic disease; suggested by:
- Serum ferritin <100 µg/L in setting of a chronic inflammatory disease
- Elevation of soluble transferrin receptor
- Absence of stainable iron on bone marrow aspiration/biopsy
- Response to a therapeutic trial of oral iron
Clinical Features
- anemia symptoms (see Anemia, H6)
- hepatosplenomegaly, hemochromatosis

Investigations
- serum iron indices
  - increased serum Fe^{2+}, normal TIBC, increased ferritin, increased sTfR
- blood film/bone marrow biopsy
  - ringed sideroblasts (diagnostic hallmark)
  - RBCs are hypochromic; can be micro-, normo-, or macrocytic
  - anisocytosis, poikilocytosis, basophilic stippling

Treatment
- depends on etiology
  - X-linked: high dose pyridoxine (vitamin B6) in some cases
  - acquired: EPO and G-CSF
  - reversible: remove precipitating cause
- supportive transfusions for severe anemia

Lead Poisoning

Definition/Etiology
- blood lead levels greater than 80 µg/dL, possible symptomatology at 50 µg/dL
- identify source: consider occupational history, exposures history

Clinical Features
- abdominal pain, constipation, irritability, difficulty concentrating

Treatment
- chelation therapy: dimercaprol and EDTA are first line agents

Thalassemia
- see Hemolytic Anemia – Thalassemia, H19

Normocytic Anemia
- MCV 80-100 fL
- see Figure 2, Approach to Anemia, H6

Aplastic Anemia

Definition
- destruction of hematopoietic cells of the bone marrow leading to pancytopenia and hypocellular bone marrow

Epidemiology
- occurs at any age
- slightly more common in males

Etiology

<table>
<thead>
<tr>
<th>Table 11. Etiology of Aplastic Anemia</th>
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<tbody>
<tr>
<td><strong>Congenital</strong></td>
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<tr>
<td>Fanconi's anemia</td>
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<td>Shwachman-Diamond syndrome</td>
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<tr>
<td>Drugs</td>
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<td>Toxins</td>
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<td>Ionizing Radiation</td>
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<td>Autoimmune (rare)</td>
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Clinical Features
- can present acutely or insidiously
- symptoms of anemia (see Anemia, H6), thrombocytopenia (see Thrombocytopenia, H7), and/or infection
- ± splenomegaly and lymphadenopathy (depending on the cause)
Investigations

- exclude other causes of pancytopenia (see Figure 4), including PNH (overlap syndrome)
- CBC
  - anemia or neutropenia or thrombocytopenia (any combination) ± pancytopenia
  - decreased reticulocytes (<1% of the total RBC count)
- blood film
  - decreased number of normal RBCs
- bone marrow
  - aplasia or hypoplasia of marrow cells with fat replacement
  - decreased cellularity

Treatment

- remove offending agents
- supportive care (red cell and platelet transfusions, antibiotics)
  - judicious use so as to not increase the risk of immune sensitization to blood products
- immunosuppression (for idiopathic aplastic anemia)
  - anti-thymocyte globulin: 50-60% of patients respond
  - cyclosporine
- allogenic bone marrow transplant
- growth factors: e.g. Eltrombopag (TPO receptor agonist)

Hemolytic Anemia

- uncommon cause for anemia (<5% of cases) with many etiologies (>200)

Classification

- hereditary
  - abnormal membrane (spherocytosis, elliptocytosis)
  - abnormal enzymes (pyruvate kinase deficiency, G6PD deficiency)
  - abnormal hemoglobin synthesis (thalassemias, hemoglobinopathies)
- acquired
  - immune
    - autoimmune: warm vs. cold autoimmune hemolytic anemias (AIHA), see Table 14 Classification of AIHA, H22
    - alloimmune: hemolytic disease of the fetus/newborn
  - non-immune
    - MAHA: thrombus in blood vessel causes RBCs to be sheared
      - associated with DIC, HUS/HTP, preeclampsia/HELLP, vasculitides, malignant hypertension
    - other causes: PNH, hypersplenism, march hemoglobinuria (exertional hemolysis), infection (e.g. malaria), snake venoms, mechanical heart valves
  - also classified as intravascular or extravascular
    - intravascular: G6PD deficiency, TTP, DIC, and PNH
    - extravascular: AIHA and membranopathies

Clinical Features Specific to HA

- jaundice
- dark urine (hemoglobinuria, bilirubin)
- cholelithiasis (pigment stones)
- potential for an aplastic crisis (i.e. BM suppression in overwhelming infection)
- iron overload with extravascular hemolysis
- iron deficiency with intravascular hemolysis

Investigations

Table 12. Investigations for Hemolytic Anemia

<table>
<thead>
<tr>
<th>Screening Tests</th>
<th>Tests Specific For Intravascular Hemolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased LDH</td>
<td>Schistocytes on blood film</td>
</tr>
<tr>
<td>Decreased haptoglobin</td>
<td>Free hemoglobin in serum</td>
</tr>
<tr>
<td>Increased unconjugated bilirubin</td>
<td>Methemalbuminemia (heme + albumin)</td>
</tr>
<tr>
<td>Increased urorbilinogen</td>
<td>Hemoglobinuria (immediate)</td>
</tr>
<tr>
<td>Reticulocytosis</td>
<td>Hemosiderinuria (delayed)</td>
</tr>
</tbody>
</table>

Tests Specific for Extravascular Hemolysis

- Direct Coombs test (direct antiglobulin test)
  - Detects IgG or complement on the surface of RBC
  - Add anti-IgG or anti-complement Ab to patient's RBCs; positive if agglutination
  - Indications: hemolytic disease of newborn, AIHA, hemolytic transfusion reaction
- Indirect Coombs test (indirect antiglobulin test)
  - Detects antibodies in serum that can recognize antigens on RBCs
  - Mix patient's serum + donor RBCs + Coombs serum (anti-human Ig Ab); positive if agglutination
  - Indications: cross-matching donor RBCs, atypical blood group, blood group Ab in pregnant women, AIHA
Thalassemia

Definition
• defects in production of the α or β chains of hemoglobin
  ▪ resulting imbalance in globin chains leads to ineffective erythropoiesis and hemolysis in the spleen or BM
• clinical manifestations and treatment depends on specific gene and number of alleles affected
• common features:
  ▪ increasing severity with increasing number of alleles involved
  ▪ hypochromic microcytic anemia
  ▪ basophilic stippling, abnormally shaped RBCs on blood film

Pathophysiology
• defect may be in any of the Hb genes
  ▪ normally 4α genes in total; 2 on each copy of chromosome 16
  ▪ normally 2β genes in total; 1 on each copy of chromosome 11
  ▪ fetal hemoglobin, HbF (α2γ2), switches to adult forms HbA (α2β2) and HbA2 (α2δ2) at 3-6 mo of life
  ▪ HbA constitutes 97% of adult hemoglobin
  ▪ HbA2 constitutes 3% of adult hemoglobin

β-Thalassemia Minor (Thalassemia Trait)

Definition
• defect in single allele of β gene (heterozygous)
• common in people of Mediterranean and Asian descent

Clinical Features
• none; a palpable spleen is very rare

Investigations
• Hb (100-140 g/L), MCV(<70), Fe (normal), RBC count (normal)
• peripheral blood film – microcytosis basophilic stippling
• Hb electrophoresis
  ▪ specific: HbA2 increased to 3.5-5% (normal 1.5-3.5%)
  ▪ non-specific: 50% have slight increase in HbF

Treatment
• no treatment required
• genetic counselling for patient and family

β-Thalassemia Major

Definition
• defect in both alleles of β gene (homozygous, autosomal recessive)

Pathophysiology
• ineffective chain synthesis leading to ineffective erythropoiesis, hemolysis of RBCs, and increase in HbF

Clinical Features
• initial presentation at age 6-12 mo when HbA normally replaces HbF
  ▪ severe anemia, jaundice
• iron overload progressing to hemochromatosis
  ▪ secondary to repeated transfusions and ineffective erythropoiesis
  ▪ leads to iron-induced organ damage (see Gastroenterology, G33)
• stunted growth and development (hypogonadal dwarf)
• gross hepatosplenomegaly (due to extramedullary hematopoiesis)
• radiologic changes (due to expanded marrow cavity) and extramedullary hematopoietic masses (erythroid tissue tumours)
  ▪ skull x-ray has “hair-on-end” appearance
  ▪ pathologic fractures common
• evidence of increased Hb catabolism (e.g. pigmented gallstones)
• death can result from
  ▪ untreated anemia (should transfuse)
  ▪ infection (should identify and treat early)
  ▪ iron overload (common): late complication from repeated transfusions and ineffective erythropoiesis
Investigations
- CBC: Hb 40-60 g/L (4-6 g/dL)
- Hb electrophoresis
  - HbA: 0-10% (normal >95%)
  - HbA2 >2.5%
  - HbF: 90-100%

Treatment
- lifelong regular transfusions to suppress endogenous erythropoiesis
- iron chelation (e.g. deferoxamine, deferasirox, deferiprone) to prevent iron overload in organs and the formation of free radicals (which promote tissue damage and fibrosis)
- folic acid supplementation if not transfused
- allogenic bone marrow transplantation
- splenectomy (now performed less frequently)

β-Thalassemia Intermedia

Definition
- clinical diagnosis in patients whose clinical manifestations are too mild to be classified as thalassemia major, but too severe to be classified as thalassemia minor

Clinical Features
- wide variety of clinical phenotypes
- in most cases of TI, both β-globin genes affected
- three main mechanisms account for the milder phenotype compared to thalassemia major: (1) subnormal (vs. absent) beta-chain synthesis, (2) increased number of gamma chains, (3) coinheritance of alpha thalassemia (in some cases)
- complications more commonly seen in TI than thalassemia major include extramedullary hematopoiesis, leg ulcers, gallstones, thrombosis, and pulmonary hypertension

α-Thalassemia

Definition
- defect(s) in α genes
- similar geographic distribution as β-thalassemia, but higher frequency among Asians and Africans

Clinical Features
- 1 defective α gene (aa/a-): clinically silent; normal Hb, normal MCV
- 2 defective α genes (cis: aa/-/ or trans: a/-/-): decreased MCV, normal Hb
  - N.B. cis 2-gene deletion more common in Asia vs. trans 2-gene deletion more common in Africa – this leads to increased risk of fetal hydrops in offspring of Asian patients vs. African patients
- 3 defective α genes (a-/-/-): HbH (β4) disease; presents in adults, decreased MCV, decreased Hb, splenomegaly
- 4 defective α genes (--/-/-): Hb Barts (γ4) disease (hydrops fetalis); usually incompatible with life

Investigations
- peripheral blood film – screen for HbH inclusion bodies with supravital stain
- Hb electrophoresis not diagnostic for α-thalassemia
- DNA analysis using α gene probes is the only way to confirm the diagnosis
- referral to genetic counselor prior to childbearing for patients with 2-gene cis deletion (or 3-gene deletion), due to risk of fetal hydrops if partner also carries thalassemia trait

Treatment
- depends on degree of anemia
  - 1 or 2 defective α genes: no treatment required
  - HbH disease: similar to β-thalassemia intermedia
  - HbBarts: intrauterine transfusion
Sickle Cell Disease

**Definition**
- Sickling disorders arise due to a mutant β-globin chain, most commonly caused by a Glu → Val substitution at position 6 (chromosome 11) resulting in HbS variant, rather than HbA (normal adult Hb).
  - Increased incidence of HbS allele with African or Mediterranean heritage (thought to be protective against malaria).
  - Sickle cell disease occurs when an individual has two HbS genes (homozygous, HbSS) or one HbS gene + another mutant β-globin gene (compound heterozygote) - most commonly HbS-β-thal and HbSC disease.

**Pathophysiology**
- At low pO2, deoxy HbS polymerizes leading to rigid crystal-like rods that distort membranes → ‘sickles’
- The pO2 level at which sickling occurs is related to the percentage of HbS present:
  - Heterozygotes (HbAS): sickling occurs at a pO2 of 40 mmHg
  - Homozygotes (HbSS): sickling occurs at a pO2 of 80 mmHg
- Sickle cell aggravation by acidemia, increased CO2, increased 2,3-DPG, fever, and osmolality.
- Fragile sickle cells then cause injury in two main ways:
  1. Fragile sickle cells hemolyze (nitric oxide depletion).
  2. Occlusion of small vessels (hypoxia, ischemia-reperfusion injury).

**Clinical Features**
- HbAS (sickle cell trait): patient will be asymptomatic except during extreme hypoxia or infection.
- Increased risk of renal medullary carcinoma.
- SCD-SS (HbSS): chronic hemolytic anemia, jaundice in the first yr of life, retarded growth and development ± skeletal changes, splenomegaly in childhood, splenic atrophy in adulthood.
- SCD-SS often presents with acute pain episode:
  1. Aplastic crises:
     - Toxins and infections (especially parvovirus B19) transiently suppress bone marrow.
  2. Spleenic sequestration crises:
     - Usually in children; significant pooling of blood in spleen resulting in acute Hb drop and shock.
     - Uncommon in adults due to asplenia from repeated infarction.
  3. Vaso-occlusive crises (infarction):
     - May affect various organs causing ischemia-reperfusion injury (especially in back, chest, abdomen, and extremities), fever, and leukocytosis.
     - Can cause a stroke or a silent myocardial infarction.
     - Precipitated by infections, dehydration, rapid change in temperature, pregnancy, menses, and alcohol.
  4. Acute chest syndrome (see sidebar).
- SCD-SC (most common compound heterozygote):
  1. 1:833 live births in African-Americans, common in West Africa.
  2. Milder anemia than HbSS.
  3. Similar complications as HbSS, although typically milder and less frequent (exception is proliferative sickle retinopathy, glomerulonephritis, and avascular necrosis).
  4. Spleen not always atrophic in adults.

**Investigations**
- Sickle cell prep (detects sickling of RBCs under the microscope in response to O2 lowering agent): determines the presence of a HbS allele, but does not distinguish HbAS from HbSS.
- Hb electrophoresis distinguishes HbAS, HbSS, HbSC, and other variants.

**Table 13. Investigations for Sickle Cell Disease**

<table>
<thead>
<tr>
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<th>HbAS</th>
<th>HbSS</th>
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<tr>
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<td></td>
<td>HbS fraction of 0.35 (35%)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 7. Pathophysiology of sickling**

**Acute Chest Syndrome**
Affects 30% of patients with sickle cell disease and may be life threatening. Presentation includes dyspnea, chest pain, fever, tachypnea, leukocytosis, and pulmonary infiltrate on CXR. Caused by vaso-occlusion, infection, or pulmonary fat embolus from infarcted marrow.

**Organs Affected by Vaso-Occlusive Crisis**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Problem</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>Ischemic or hemorrhagic stroke, vasculopathy</td>
</tr>
<tr>
<td>Eye</td>
<td>Hemorrhage, blindness</td>
</tr>
<tr>
<td>Liver</td>
<td>Infarcts, RUG syndrome</td>
</tr>
<tr>
<td>Lung</td>
<td>Chest syndrome, long-term pulmonary hypertension</td>
</tr>
<tr>
<td>Gallbladder</td>
<td>Stones</td>
</tr>
<tr>
<td>Heart</td>
<td>Hyperdynamic flow murmurs</td>
</tr>
<tr>
<td>Spleen</td>
<td>Enlarged (child); atrophic (adult)</td>
</tr>
<tr>
<td>Kidney</td>
<td>Hematuria, loss of renal concentrating ability, proteinuria</td>
</tr>
<tr>
<td>Intestines</td>
<td>Acute abdomen</td>
</tr>
<tr>
<td>Placenta</td>
<td>Stillbirths</td>
</tr>
<tr>
<td>Penis</td>
<td>Priapism</td>
</tr>
<tr>
<td>Digits</td>
<td>Dactylitis</td>
</tr>
<tr>
<td>Femoral and Humeral Head</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>Infarction, infection</td>
</tr>
<tr>
<td>Ankle</td>
<td>Leg ulcers</td>
</tr>
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<td></td>
<td>HbS fraction of 0.35 (35%)</td>
<td></td>
</tr>
</tbody>
</table>
Treatment

- genetic counselling
- HbAS: no treatment required
- HbSC: treatment as per HbSS, but is dictated by symptom severity
- HbSS
  1. folic acid to prevent folate deficiency
  2. hydroxyurea to enhance production of HbF
     - mechanism of action: stops repression of Hb-γ chains and/or initiates differentiation of stem cells in which this gene is active
     - presence of HbF in the SS cells decreases polymerization and precipitation of HbS
     - N.B. hydroxyurea is cytotoxic and may cause bone marrow suppression
  3. treatment of vaso-occlusive crisis
     - oxygen
     - hydration (reduces viscosity)
     - correct acidosis
     - analgesics/opiates
     - indication for exchange transfusion: acute chest syndrome, stroke, multi-organ failure, ICU admission
     - less routinely: antimicrobials for suspected infection
  4. prevention of crises
     - establish diagnosis
     - avoid conditions that promote sickling (hypoxia, acidosis, dehydration, fever)
     - vaccination in childhood (pneumococcus, meningococcus, *H. influenza b*)
     - prophylactic penicillin (age 3 mo-5 yr)
     - good hygiene, nutrition, and social support
  5. screen for complications
     - regular blood work (CBC, reticulocytes, iron indices, BUN, LFTs, creatinine)
     - urinalysis annually (proteinuria, glomerulopathy)
     - transcranial doppler annually until 16 yr old (stroke prevention)
     - retinal examinations annually from 8 yr old (screen for retinopathy)
     - echocardiography starting at 10 yr old (screen for pulmonary hypertension)

Autoimmune Hemolytic Anemia

<table>
<thead>
<tr>
<th>Table 14. Classification of AIHA</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td><strong>Warm</strong></td>
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<tr>
<td><strong>Cold</strong></td>
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<tr>
<td><strong>Antibody Allotype</strong></td>
</tr>
<tr>
<td><strong>Agglutination Temperature</strong></td>
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<tr>
<td><strong>Direct Coombs Test</strong></td>
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<tr>
<td><strong>Etiology</strong></td>
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<td><strong>Blood Film</strong></td>
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<td><strong>Management</strong></td>
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<tr>
<td><strong>Agglutination</strong></td>
</tr>
</tbody>
</table>

Microangiopathic Hemolytic Anemia

**Definition**
- hemolytic anemia due to intravascular fragmentation of RBCs

**Etiology**
- see *Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome*, H30
- see *Disseminated Intravascular Coagulation*, H32
- eclampsia, HELLP syndrome, AFLP (see *Obstetrics*, OB25, OB26)
- malignant hypertension
- vasculitis
- malfunctioning heart valves
- metastatic carcinoma
- drugs (calcineurin inhibitors, quinine, simvastatin)
- infections (severe CMV or meningococcus)
- catastrophic antiphospholipid antibody syndrome

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NIH Consensus Development Conference
Statement: Hydroxyurea Treatment for Sickle Cell Disease
**Efficacy**: Strong evidence for adolescents and adults and there is emerging data supporting its use in children. In the single RCT, the Hb level was higher in hydroxyurea recipients than placebo recipients after 2 yr (difference, 6 g/L), as was HbF (absolute difference, 3.2%). The median number of painful crises was 44% lower than in the placebo arm. The 12 observational studies that enrolled adults reported a relative increase in HbF of 0-20% and a relative reduction in crisis rates by 68-84%. Hospital admissions declined by 18-32%.
**Effectiveness**: Data is limited. It seems to be highly effective but is currently underutilized.
**Short-Term Harms (within 6 mo)**: Dose-related leukopenia, thrombocytopenia, anemia, and decreased reticulocyte count. Others include decreased sperm production and dry skin.
**Long-Term Harms**: Birth defects in offspring of people receiving the drug, growth delays in children receiving the drug, and cancer in both children and adults who receive the drug.
Investigations
- blood film: evidence of hemolysis, schistocytes
- hemolytic workup
- urine: hemosiderinuria, hemoglobinuria

Hereditary Spherocytosis
- most common type of hereditary hemolytic anemia
- abnormality in RBC membrane proteins (e.g. spectrin)
- spleen makes defective RBCs more spherocytotic (and more fragile) by membrane removal; also acts as site of RBC destruction
- autosomal dominant with variable penetrance

Investigations
- blood film (shows spherocytes), osmotic fragility (increased), molecular analysis for spectrin gene

Treatment
- in severe cases, splenectomy and vaccination against pneumococcus, meningococcus, and H. influenza b (avoid in early childhood)

Hereditary Elliptocytosis
Definition/Etiology
- abnormality in spectrin interaction with other membrane proteins
- autosomal dominant
- 25-75% elliptocytes
- hemolysis is usually mild

Treatment
- immunizations; splenectomy for severe hemolysis

Glucose-6-Phosphate Dehydrogenase Deficiency
Definition
- deficiency in glucose-6-phosphate dehydrogenase (G6PD), corresponding to a lack of reduced glutathione (GSH) and leading to RBC sensitivity due to oxidative stress

Pathophysiology
- X-linked recessive, prevalent in individuals of African, Asian, and Mediterranean descent

Clinical Features
- frequently presents as episodic hemolysis precipitated by:
  - oxidative stress
  - drugs (e.g. sulfonamide, antimalarials, nitrofurantoin)
  - infection
  - food (fava beans)
- in neonates: can present as prolonged, pathologic neonatal jaundice

Investigations
- neonatal screening
- G6PD assay (may not be useful if result is normal)
  - should not be done in acute crisis when reticulocyte count is high (reticulocytes have high G6PD levels)
- blood film
  - Heinz bodies (granules in RBCs due to oxidized Hb); passage through spleen results in the generation of bite cells
  - may have features of intravascular hemolysis (e.g. RBC fragments)

Treatment
- folic acid
- stop offending drugs and avoid triggers
- transfusion in severe cases
Macrocytic Anemia

- MCV >100 fL
- see Figure 2, Approach to Anemia, H6

Table 15. Comparison Between Megaloblastic and Non-Megaloblastic Macrocytic Anemia

<table>
<thead>
<tr>
<th></th>
<th>Megaloblastic</th>
<th>Non-Megaloblastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td>Large, oval, nucleated RBC precursor</td>
<td>Large round RBC</td>
</tr>
<tr>
<td></td>
<td>Hypersegmented neutrophils</td>
<td>Normal neutrophils</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Failure of DNA synthesis resulting in</td>
<td>Reflects membrane abnormality with abnormal cholesterol metabolism</td>
</tr>
<tr>
<td></td>
<td>asynchronous maturation of RBC nucleus and cytoplasm</td>
<td></td>
</tr>
</tbody>
</table>

Vitamin B₁₂ Deficiency

B₁₂ (cobalamin) see Gastroenterology, G17 and Family Medicine – Nutrition, FM5

- binds to intrinsic factor (IF) secreted by gastric parietal cells
- absorbed in terminal ileum
- total body stores sufficient for 3-4 yr

Etiology

Table 16. Etiology of Vitamin B₁₂ Deficiency

<table>
<thead>
<tr>
<th>Diet</th>
<th>Gastric</th>
<th>Intestinal Absorption</th>
<th>Genetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strict vegan</td>
<td>Mucosal atrophy</td>
<td>Malabsorption</td>
<td>Transcobalamin</td>
</tr>
<tr>
<td>Vegetarian in pregnancy</td>
<td>Gastritis, autoimmune</td>
<td>Crohns, celiac sprue, pancreatic insufficiency</td>
<td>II deficiency</td>
</tr>
<tr>
<td></td>
<td>Pernicious anemia (see below)</td>
<td>Stagnant bowel</td>
<td>Stomach, loop, stricture</td>
</tr>
<tr>
<td></td>
<td>Post-gastrectomy</td>
<td>Fish tapeworm</td>
<td>Fish tapeworm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Resection of ileum</td>
<td>Resection of ileum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
<td>Drugs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neomycin, biguanides, PPI, N₂O anesthesia</td>
<td>Neomycin, biguanides, PPI, N₂O anesthesia</td>
</tr>
</tbody>
</table>

Pathophysiology of Pernicious Anemia

- auto-antibodies produced against gastric parietal cells leading to achlorhydria and lack of intrinsic factor secretion
- intrinsic factor is required to stabilize B₁₂ as it passes through the bowel
- decreased intrinsic factor leads to decreased ileal absorption of B₁₂
- may be associated with other autoimmune disorders (polyglandular endocrine insufficiency)
- F:M = 1.6:1; often >60 yr old

Clinical Features

- neurological
  - cerebral (common, reversible with B₁₂ therapy)
  - confusion, delirium, dementia
  - cranial nerves (rare)
  - optic atrophy
  - cord (irreversible damage)
  - subacute combined degeneration
    - posterior columns: decreased vibration sense, proprioception, and 2-point discrimination
    - pyramidal tracts: spastic weakness, hyperactive reflexes
  - peripheral neuropathy (variable reversibility)
  - usually symmetrical, affecting lower limbs more than upper limbs

Investigations

- CBC, reticulocyte count
  - anemia often severe ± neutropenia ± thrombocytopenia
  - MCV >110 fL
  - low reticulocyte count relative to the degree of anemia (<2%)
- serum B₁₂ and RBC folate
  - caution: low serum B₁₂ leads to low RBC folate because of failure of folate polyglutamate synthesis in the absence of B₁₂
  - alternatively, can measure elevated urine metabolites (methylmalonate, homocysteine)
- blood film
  - oval macrocytes, hypersegmented neutrophils
  - oral Vitamin B₁₂ vs. Intramuscular Vitamin B₁₂ for Vitamin B₁₂ Deficiency

Cochrane DB Syst Rev 2005;3:CD004655

Study: Systematic review. 2 RCTs met inclusion criteria; total 108 patients with follow-up from 90 d-4 mo.

Intervention: One study evaluated 1,000 µg of oral B₁₂ compared to 1,000 µg IM B₁₂ on the same dosing schedule. The other compared 2,000 µg daily oral B₁₂ to 1,000 µg IM B₁₂ on a less frequent dosing schedule. Neurological and hematological end points were evaluated.

Results: Meta-analysis was not attempted due to study heterogeneity. Both studies reported improvements in hematological and neurological end-points in both oral and IM groups. No significant difference was observed between groups in either study.

Conclusions: Limited data suggests high dose oral vitamin B₁₂ (1,000-2,000 µg) is equivalent to IM vitamin B₁₂ on the same or less frequent dosing schedule. This data is severely limited by small sample sizes and short follow-up periods. Insufficient numbers of patients with malabsorption conditions were included to generalize these results to the entire primary care population.
• bone marrow
  - hypercellularity
  - nuclear-cytoplasmic asynchrony in RBC precursors (less mature nuclei than expected from the development of the cytoplasm)
• bilirubin and LDH
  - elevated unconjugated bilirubin and LDH due to breakdown of cells in BM
• Schilling test to distinguish pernicious anemia from other causes
  - anti-intrinsic factor antibody, anti-parietal cell antibody

**Treatment**
• vitamin B₁₂ 1,000 µg IM monthly for life or 1,000-1,200 µg PO daily if intestinal absorption intact
• less frequent, higher doses may be as effective (e.g. 1,000 µg IM q3mo)
• watch for hypokalemia and rebound thrombocytosis when treating severe megaloblastic anemia

### Folate Deficiency

- uncommon in developed countries due to extensive dietary supplementation (enriched in flour)
- folate stores are depleted in 3-6 mo
- folate commonly found in green, leafy vegetables and fortified cereals

**Etiology**

**Table 17. Etiology of Folate Deficiency**

<table>
<thead>
<tr>
<th>Diet/Deficiency</th>
<th>Malabsorption</th>
<th>Drugs</th>
<th>Increased Demand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism Subst. abuse</td>
<td>Celiac sprue IBD</td>
<td>Anti-folates (methotrexate)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Elderly/infants Poor intake</td>
<td>Infiltrative bowel disease Short bowel syndrome</td>
<td>Anticonvulsants (phenytoin) Alcohol Oral contraceptive</td>
<td>Hemolysis Prematurity Exfoliative dermatitis/psoriasis Hemodialysis</td>
</tr>
</tbody>
</table>

**Clinical Features**
- mild jaundice due to hemolysis of RBCs secondary to ineffective hemoglobin synthesis
- glossitis and angular stomatitis
- melanin pigmentation (rare)
- purpura secondary to thrombocytopenia (rare)
- unlike B₁₂ deficiency, folate deficiency has no neurologic manifestations

**Investigations**
- similar to B₁₂ deficiency (CBC, reticulocytes, blood film, RBC folate, serum B₁₂)
- if decreased RBC folate, rule out B₁₂ deficiency as cause

**Management**
- folic acid 1-5 mg PO OD x 1-4 mo; then 1 mg PO OD maintenance if cause is not reversible

### Hemostasis

**Three Phases of Hemostasis**

1. **Primary Hemostasis**
   - goal is rapid cessation of bleeding; main effect is on mucocutaneous bleeding
   - vessel injury results in collagen/subendothelial matrix exposure and release of vasoconstrictors
   - blood flow is impeded and platelets come into contact with damaged vessel wall (Figure 11a)
     - adhesion: platelets adhere to subendothelium via von Willebrand factor (vWF)
     - activation: platelets are activated resulting in change of shape and release of ADP and thromboxane A₂
     - aggregation: these factors further recruit and aggregate more platelets resulting in formation of localized hemostatic plug

2. **Secondary Hemostasis**
   - platelet plug is reinforced by production of fibrin clot (Figure 11b)
   - extrinsic pathway: initiation of coagulation *in vivo*
   - intrinsic pathway: amplification once coagulation has started

3. **Fibrin Stabilization and Fibrinolysis (resolution)**
   - conversion from soluble to insoluble clot
   - once healing initiated, clot dissolution (anticoagulant pathway)
Table 18. Commonly Used Tests of Hemostasis

<table>
<thead>
<tr>
<th>Type of Hemostasis</th>
<th>Test</th>
<th>Reference Range</th>
<th>Purpose</th>
<th>Examples of Associated Diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary</strong></td>
<td>Platelet count</td>
<td>150-400 x 10^9/L</td>
<td>To quantitate platelet number</td>
<td>Low in ITP, HUS/TTP, DIC</td>
</tr>
<tr>
<td></td>
<td>aPTT</td>
<td>22-35 s</td>
<td>Measures intrinsic pathway (factors VIII, IX, XI, XII) and common pathway</td>
<td>Prolonged in hemophilias A and B</td>
</tr>
<tr>
<td></td>
<td>PT</td>
<td>11-24 s</td>
<td>Measures extrinsic pathway (factor VII in particular) and common pathway</td>
<td>Prolonged in factor VII deficiency</td>
</tr>
<tr>
<td></td>
<td>INR</td>
<td>0.9-1.2</td>
<td>Only used to monitor warfarin therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary</strong></td>
<td>Mixing studies</td>
<td>Differentiate inhibitors of clotting factor(s) from a deficiency in clotting factor(s)</td>
<td>Clotting factor(s) deficiency if test becomes normal</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mix patient’s plasma with normal plasma in 1:1 ratio and repeat abnormal test</td>
<td>Inhibitors of clotting factor(s) if test still abnormal</td>
<td></td>
</tr>
<tr>
<td><strong>Fibrinolysis</strong></td>
<td>Euglobulin lysis time</td>
<td>N &gt; 90 min</td>
<td>Looks for accelerated fibrinolysis</td>
<td>May be accelerated in DIC or factor XIII deficiency</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Fibrinogen</td>
<td></td>
<td></td>
<td>Decreased in hereditary deficiency of fibrinogen</td>
</tr>
<tr>
<td></td>
<td>Fibrinogen degradation products (FDPs), D-dimers</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Specific factor assays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tests of physiological inhibitors (antithrombin, protein S, protein C, hereditary resistance to activated protein C [APC])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tests of pathologic inhibitors (e.g. lupus anticoagulant)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 19. Signs and Symptoms of Disorders of Hemostasis

<table>
<thead>
<tr>
<th></th>
<th>Primary (Platelet)</th>
<th>Secondary (Coagulation)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Surface Cuts</strong></td>
<td>Excessive, prolonged bleeding</td>
<td>Normal/slightly prolonged bleeding</td>
</tr>
<tr>
<td><strong>Onset After Injury</strong></td>
<td>Immediate</td>
<td>Delayed</td>
</tr>
<tr>
<td><strong>Site of Bleeding</strong></td>
<td>Superficial i.e. mucosal (nasal, gingival, GI tract, uterine), skin</td>
<td>Deep i.e. joints, muscles, GI tract, GU tract</td>
</tr>
<tr>
<td><strong>Lesions</strong></td>
<td>Petechiae, ecchymoses</td>
<td>Hemarthroses, hematomas</td>
</tr>
</tbody>
</table>
Table 20. Lab Values in Disorders of Hemostasis

<table>
<thead>
<tr>
<th></th>
<th>PT</th>
<th>PTT</th>
<th>Platelet Count</th>
<th>RBC Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A/B</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>vWD</td>
<td>N</td>
<td>±</td>
<td>N/4</td>
<td>N</td>
</tr>
<tr>
<td>DIC</td>
<td>↑</td>
<td>±</td>
<td>↓</td>
<td>N/4</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>↑</td>
<td>N/4</td>
<td>N/4</td>
<td>N</td>
</tr>
<tr>
<td>ITP</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>TTP</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; ITP = idiopathic thrombocytopenic purpura; TTP = thrombotic thrombocytopenic purpura; vWD = von Willebrand disease

Disorders of Primary Hemostasis

Definition
- inability to form an adequate platelet plug due to
  - disorders of blood vessels
  - disorders of platelets: abnormal function/numbers
  - disorders of vWF

Classification

![Figure 13. Approach to disorders of primary hemostasis]

Immune Thrombocytopenic Purpura

Table 21. Immune Thrombocytopenic Purpura

<table>
<thead>
<tr>
<th>Features</th>
<th>Acute ITP</th>
<th>Chronic ITP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak Age</td>
<td>2-6 yr</td>
<td>20-40 yr</td>
</tr>
<tr>
<td>Gender</td>
<td>None</td>
<td>F&gt;M (2:1)</td>
</tr>
<tr>
<td>History of Recent Infection</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Onset of Bleed</td>
<td>Abrupt</td>
<td>Insidious</td>
</tr>
<tr>
<td>Duration</td>
<td>Usually wk</td>
<td>Months to yr</td>
</tr>
<tr>
<td>Spontaneous Remissions</td>
<td>80% or more</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

ACUTE (CHILD-TYPE) ITP
- see Pediatrics, P49

CHRONIC (ADULT-TYPE) ITP
- most common cause of isolated thrombocytopenia
- diagnosis of exclusion (i.e. isolated thrombocytopenia [platelets <100,000/mm³] and the absence of any obvious initiating and/or underlying cause)
**Pathophysiology**
- an acquired immune-mediated disorder
  - anti-platelet antibodies bind to platelet surface \(\rightarrow\) increased splenic destruction and clearance
  - impaired platelet production
  - helper T-cell and cytotoxic T-cell activation also implicated in platelet destruction

**Clinical Presentation**
- can present asymptomatic, with minimal bruising, or serious bleed (GI bleed, skin and mucosal hemorrhage or intracranial hemorrhage), lethargy, fatigue

**Investigations**
- CBC and reticulocyte count: thrombocytopenia (request retic count if not an isolated thrombocytopenia)
- PT and aPTT: normal
- peripheral blood film: decreased platelets, giant platelets (rule out platelet clumping)
- HIV, HCV serology (if risk factors are present)
- vitamin B12, ANA, C3, C4, depending on clinical symptoms
- bone marrow aspirate and biopsy: increased number of megakaryocytes
- recommended in patients >60 yr of age, pre-splenectomy or have failed multiple lines of ITP treatment, those with systemic symptoms, an abnormal blood film, and/or abnormal signs to rule out other causes of thrombocytopenia (e.g. myelodysplasia)

**Treatment**
- rarely indicated if platelet <30 x 10^9/L unless active bleeding, trauma, or surgery
- emergency treatment (active bleeding [CNS, GI, or GU] or in need of emergency surgery)
  - general measures: stop drugs reducing platelet function, control blood pressure, minimize trauma
  - corticosteroids: prednisone (1 mg/kg) or methylprednisolone (1 g/d x 3 d) or dexamethasone (40 mg PO x 4 d)
  - antifibrinolytic: tranexamic acid (1 g PO tid or 1 g IV q6h) if refractory bleeding
  - IVlg 1 g/kg/d x 2 doses, or 2 g/kg over 5 d
  - platelet transfusion: for life-threatening bleeding
  - emergency splenectomy: may be considered, vaccinations prior (pneumococcus, meningococcus, H. influenza b) management of intracranial bleeding: IV steroids, IVlg, platelets, emergency splenectomy, and then craniotomy; maintain Plt >100 for at least 7 wk post intracranial hemorrhage
- non-urgent treatment (platelet count <20-30 x 10^9/L and no bleeding OR platelet count <50 x 10^9 and significant bleeding)
  - platelet transfusion does not work
  - 1st line
    - corticosteroids (dexamethasone 40 mg/d x 4 wk or prednisone 1 mg/kg/d)
    - IVlg
    - anti-D: appropriate for Rh+ non-splenectomized patients, but can cause hemolysis (avoid if low Hb at baseline or if DAT is positive)
  - 2nd line
    - splenectomy (need vaccinations prior to splenectomy: pneumococcus, meningococcus, H. influenza b)
    - immunosuppressants (azathioprine, cyclophosphamide)
    - rituximab
    - danazol, vincristine
    - thrombopoietin (TPO) receptor agonists (romiplostim, eltrombopag)

**Prognosis**
- ~20% will not attain a hemostatic platelet count after first and second line therapy
- fluctuating course
- overall relatively benign, mortality 1-2%
- major concern is cerebral hemorrhage at Plt <5 x 10^9/L, although very rare

---

**Heparin-Induced Thrombocytopenia**
- heparin-induced thrombocytopenia (previously known as HIT type II): immune-mediated reaction following treatment with heparin leading to coagulation activation
- heparin-associated thrombocytopenia (previously known at HIT type I): transient thrombocytopenia following administration of heparin

**Mechanisms for HIV-associated Thrombocytopenia**
- Direct effect of HIV on marrow
- Immune-mediated platelet destruction
- Some anti-retrovirals reduce platelet production

**Should Rituximab Be Used Before or After Splenectomy in Patients with Immune Thrombocytopenic Purpura (ITP)?**
- Curr Opin Hematol 2007;14:642-646

**Purpose:** To determine whether the optimal timing for rituximab is before splenectomy, or after failure of splenectomy.

**Results:** Rituximab produces an initial response in approximately 60% of cases, with no significant difference between splenectomized and non-splenectomized patients. Long-term complete responses are observed in 15-20% of cases. Adverse events related to the drug were usually mild or moderate, with a low incidence of infections. Long-term safety data, however, are still lacking. Deaths have been reported for 2.9% of ITP cases treated with rituximab, but they could not be attributed to the study drug.

**Conclusion:** Both the response rate and the response duration appear lower following rituximab than following splenectomy. Although the side effects may be fewer, there is insufficient evidence to support the replacement of splenectomy with rituximab as a second-line treatment of chronic ITP outside a clinical trial. At the present time, the use of immunotherapy before splenectomy can be recommended only in patients at high risk for splenectomy and those not willing to undergo surgery.
### Table 22. Heparin-Induced Thrombocytopenia (HIT)

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Immune mediated Ab recognizes a complex of heparin and platelet factor 4 (PF4) leading to platelet activation via platelet Fc receptor and activation of coagulation system</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>50% reduction in platelets while on heparin within 5-15 wk of initiation</td>
</tr>
<tr>
<td>Onset of Decreased Platelets</td>
<td>5-15 wk (if previously exposed to heparin, HIT can develop in hours)</td>
</tr>
<tr>
<td>Risk of Thrombosis</td>
<td>~30% (25% of events are arterial)</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Bleeding complications uncommon Venous thrombosis: DVT, PE, limb gangrene, cerebral sinus thrombosis Arterial thrombosis: MI, stroke, acute limb ischemia, organ infarct (mesentery, kidney) Heparin-induced skin necrosis (with LMWH) Acute platelet activation syndromes: acute inflammatory reactions (e.g. fever/chills, flushing, etc.) Transient global amnesia (rare)</td>
</tr>
<tr>
<td>Specific Tests</td>
<td>Pre-test clinical scoring models can help rule-out HIT: 4-Ts (see Table 23) and the HIT Expert Probability (HEP) score 14C serotonin release assay (uses donor platelets with 14C serotonin and heparin with patient’s plasma) ELISA for HIT-Ig (more sensitive, less specific than serotonin assay) Ultrasound of lower limb veins for DVT</td>
</tr>
<tr>
<td>Management</td>
<td>Clinical suspicion of HIT should prompt discontinuation of heparin and LMWH (specific tests take several days) Initiate anticoagulation with a non-heparin anticoagulant: e.g. argatroban, danaparoid, fondaparinux, bivalirudin unless there is a strong contraindication (duration of treatment at least 2-3 mo if no thrombotic event, and at least 3-6 mo if thrombotic event has occurred) Warfarin should only be restarted when platelet count &gt;100 x 10^9/L Allergy band and alert in patient records</td>
</tr>
</tbody>
</table>

LMWH is also associated with HIT, but the risk is less than unfractionated heparin (2.6% in UFP vs. 0.2% in LMWH)

### Table 23. The 4-T Pre-Test Clinical Scoring Model for HIT

<table>
<thead>
<tr>
<th>Category</th>
<th>2 Points</th>
<th>1 Point</th>
<th>0 Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Thrombocytopenia</td>
<td>Platelet count fall &gt;50% AND platelet nadir ≥20 x 10^9/L</td>
<td>Platelet count fall 30-50% OR platelet nadir 10-19 x10^9/L</td>
<td>Platelet count fall &lt;30% OR platelet nadir &lt;10 x10^9/L</td>
</tr>
<tr>
<td>2. Timing of Platelet Count Fall</td>
<td>Clear onset between 5-10 d of heparin exposure OR platelet count fall at ≤1 d if prior heparin exposure within last 30 d</td>
<td>Consistent with fall in platelet count at 5-10 d but unclear (e.g. missing platelet counts) OR onset after day 10 OR fall ≤1 d with prior heparin exposure within 30-100 d</td>
<td>Platelet count fall after &lt;4 d of heparin exposure, and no recent heparin</td>
</tr>
<tr>
<td>3. Thrombosis or Other Sequelae</td>
<td>Confirmed new thrombosis, skin necrosis, or acute systemic reaction after IV unfractionated heparin bolus</td>
<td>Progressive or recurrent thrombosis, non-necrotizing (erythematous) skin lesions, or suspected thrombosis that has not been proven</td>
<td>None</td>
</tr>
<tr>
<td>4. Other Causes for Thrombocytopenia</td>
<td>None apparent</td>
<td>Possible</td>
<td>Definite</td>
</tr>
</tbody>
</table>

6-8 points = high probability of HIT; 4-5 points = intermediate probability of HIT; 0-3 points = low probability of HIT

J Thromb Haemost 2006;4:759-765
Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome

Table 24. TTP and HUS

<table>
<thead>
<tr>
<th>TTP</th>
<th>HUS (See Pediatrics, P78)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Predominantly adult</td>
</tr>
<tr>
<td>Etiology</td>
<td>Deficiency of metalloproteinase that breaks down ultra-large vWF multimers</td>
</tr>
<tr>
<td></td>
<td>• Congenital (genetic absence of ADAMTS-13)</td>
</tr>
<tr>
<td></td>
<td>• Acquired (drugs, malignancy, transplant, HIV-associated, idiopathic)</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>1. Thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>2. MAHA</td>
</tr>
<tr>
<td></td>
<td>3. Renal failure</td>
</tr>
<tr>
<td></td>
<td>4. Neurological symptoms: headache, confusion, focal defects, seizures</td>
</tr>
<tr>
<td></td>
<td>5. Fever</td>
</tr>
<tr>
<td>Investigations (both TTP, HUS)</td>
<td>CBC and blood film: decreased platelets and schistocytes</td>
</tr>
<tr>
<td></td>
<td>PT, aPTT, fibrinogen: normal</td>
</tr>
<tr>
<td></td>
<td>Markers of hemolysis: increased unconjugated bilirubin, increased LDH, decreased haptoglobin</td>
</tr>
<tr>
<td></td>
<td>Negative Coombs test</td>
</tr>
<tr>
<td></td>
<td>Creatinine, urea, to follow renal function</td>
</tr>
<tr>
<td></td>
<td>Stool C&amp;S (HUS)</td>
</tr>
<tr>
<td>Management (both TTP, HUS)</td>
<td>Medical emergency</td>
</tr>
<tr>
<td></td>
<td>Plasmapheresis ± steroids</td>
</tr>
<tr>
<td></td>
<td>Platelet transfusion is contraindicated (increased microvascular thrombosis)</td>
</tr>
<tr>
<td></td>
<td>Plasma infusion if plasmapheresis is not immediately available</td>
</tr>
<tr>
<td></td>
<td>TTP mortality ~90% if untreated</td>
</tr>
</tbody>
</table>

von Willebrand Disease

Pathophysiology
- most common inheritable coagulation abnormality
- heterogeneous group of defects, usually mild in severity
- usually autosomal dominant (type 3 is autosomal recessive)
- qualitative or quantitative abnormality of vWF
  - vWF needed for platelet adhesion and acts as carrier for Factor VIII; abnormality of vWF can affect both primary and secondary hemostasis
  - vWF exists as a series of multimers ranging in size
    - largest multimers are most active in mediation of platelet adhesion, both large and small multimers complex with Factor VIII

Classification
- type 1: mild quantitative defect (decreased amount of vWF and proportional decrease in vWF activity) – 75% of cases
- type 2: qualitative defect (vWF activity disproportionally lower than quantity) – 20-25% of cases
- type 3: severe total quantitative defect (no vWF produced) – rare

Clinical Features
- mild
  - asymptomatic
  - mucosal and cutaneous bleeding, easy bruising, epistaxis, menorrhagia
- moderate to severe
  - as above but more severe, occasionally soft-tissue hematomas, petechiae (rare), GI bleeding, hemarthroses

Investigations

Table 25. Investigations in vWD

<table>
<thead>
<tr>
<th>Test</th>
<th>Expected Result</th>
<th>Test</th>
<th>Expected Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTT</td>
<td>N/↑</td>
<td>von Willebrand antigen</td>
<td>↓</td>
</tr>
<tr>
<td>Factor VIII</td>
<td>N/↓</td>
<td>Blood group</td>
<td>Affects antigen quantification (↓ in group O)</td>
</tr>
<tr>
<td>PHe Count</td>
<td>N/↑</td>
<td>vWF multimer analysis</td>
<td>Multimer variants</td>
</tr>
<tr>
<td>Ristocetin Activity</td>
<td>↓ (cofactor for vWF-Pit binding)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pathophysiology of TTP
- vWF secreted by endothelial cells is a very large polymer rapidly cleaved by the ADAMTS-13 protease
- Congenital TTP is due to a deficiency in ADAMTS-13
- Antibodies against ADAMTS-13 are present in acquired TTP

Differential Diagnosis of TTP
- Sepsis
- DIC
- HELLP
- Antiphospholipid Ab syndrome
- Evans syndrome (AIHA + ITP)

Consider vWD in all women with menorrhagia

vWD is the most common inheritable coagulation abnormality
Treatment
- desmopressin (DDAVP) is treatment of choice for type 1 vWD
  - causes release of vWF and Factor VIII from endothelial cells
  - variable efficacy depending on disease type; tachyphylaxis occurs
  - need good response before using with further bleeding
  - caution in children due to hyponatremia
- tranexamic acid (Cyklokapron, antifibrinolytic) to stabilize clot formation
- high-purity Factor VIII concentrate containing vWF (Hemate P) in select cases
  - frozen plasma (FP) is not useful
  - need to monitor vWF and factor VIII levels (very high factor VIII level can cause thrombosis)
- conjugated estrogens (increase vWF levels)

Prognosis
- may fluctuate, often improves during pregnancy, inflammation, and with age

Disorders of Secondary Hemostasis

Definition
- inability to form an adequate fibrin clot
  - disorders of clotting factors or co-factors
  - disorders of proteins associated with fibrinolysis
- characterized by delayed bleeding, deep muscular bleeding, spontaneous joint bleeding

Table 26. Classification of Secondary Hemostasis Disorders

<table>
<thead>
<tr>
<th>Hereditary</th>
<th>Acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Factor VIII: Hemophilia A, vWD</td>
<td>Liver disease</td>
</tr>
<tr>
<td>Factor IX: Hemophilia B (Christmas Disease)</td>
<td>DIC</td>
</tr>
<tr>
<td>Factor XI</td>
<td>Vitamin K deficiency</td>
</tr>
<tr>
<td>Other factor deficiencies are rare</td>
<td>Acquired inhibitors</td>
</tr>
</tbody>
</table>

Hemophilia A (Factor VIII Deficiency)

Pathophysiology
- X-linked recessive, 1/5,000 males
- mild (>5% of normal factor level), moderate (1-5%), severe (<1%)

Clinical Features
- see Table 19 – Signs and Symptoms of Disorders of Hemostasis, H26
- older patients may also have HIV or HCV from contaminated blood products

Investigations
- prolonged aPTT, normal INR (PT)
- decreased Factor VIII (<40% of normal)
- vWF usually normal or increased

Treatment
- desmopressin (DDAVP) in mild hemophilia A
- recombinant Factor VIII concentrate for:
  - prophylaxis (2-3x/wk at home)
  - minor but not trivial bleeding (e.g. hemarthroses)
  - major potentially life-threatening bleeding (e.g. multiple trauma)
- anti-fibrinolytic agents (e.g. tranexamic acid)

Hemophilia B (Factor IX Deficiency)

- also known as Christmas disease
- X-linked recessive, 1/30,000 males
- clinical and laboratory features identical to hemophilia A (except decreased Factor IX)
- treatment: recombinant Factor IX concentrate, anti-fibrinolytic agents

Factor XI Deficiency

- also known as Rosenthal syndrome
- autosomal recessive; more common in Ashkenazi Jewish population
- usually mild, often diagnosed in adulthood
- Factor XI level does not correlate with bleeding risk
- treatment: frozen plasma, Factor XI concentrate
Liver Disease

- see Gastroenterology, G28

Pathophysiology

- deficient synthesis of all factors except VIII (also made in endothelium and in acute phase response)
- aberrant synthesis of fibrinogen
- deficient clearance of hemostatic ‘debris’ and fibrinolytic activators
- accelerated destruction due to dysfibrinogenemias: increased fibrinolysis, DIC
- miscellaneous: inhibition of secondary hemostasis by FDPs

Investigations

- peripheral blood film: target cells
- primary hemostasis affected
  - thrombocytopenia due to hypersplenism, folate deficiency, alcohol intoxication, DIC, decreased production of thrombopoietin
  - platelet dysfunction (e.g. alcohol abuse)
- secondary hemostasis affected
  - elevated INR (PT), aPTT and TT, low fibrinogen in end-stage liver disease

Treatment

- supportive, treat liver disease, blood products if active bleeding (frozen plasma, platelets, cryoprecipitate)

Vitamin K Deficiency

Etiology

- drugs
  - oral anticoagulants which inhibit Factors II, VII, IX, X, proteins C and S
  - antibiotics eradicating gut flora, altering vitamin K uptake
- poor diet (especially in alcoholics)
- biliary obstruction
- chronic liver disease (decreased stores)
- malabsorption (e.g. celiac disease)
- hemorrhagic disease of newborn, see Pediatrics, P68

Investigations

- INR (PT) is elevated out of proportion to elevation of the aPTT
- decreased Factors II, VII, IX, X (vitamin K-dependent)

Treatment

- hold anticoagulant
- vitamin K 1 mg PO for INR between 4.5-10 and no active bleeding (excludes hemorrhagic disease of the newborn)
- if bleeding, give vitamin K 10 mg IV
- if life-threatening bleeding and vitamin K antagonist used, give frozen plasma (FP) or prothrombin complex concentrate (PCC)
- PCCs are contraindicated if there is a previous history of HIT
- use FFP if PCC is contraindicated or unavailable
- note: excessive vitamin K will delay therapeutic warfarin anticoagulation once re-started

Disseminated Intravascular Coagulation

Definition

- uncontrolled release of plasmin and thrombin leading to intravascular coagulation and depletion of platelets, coagulation factors and fibrinogen
- risk of life-threatening hemorrhage

Etiology

- occurs as a complication of many other conditions
- widespread endothelial damage ± extensive inflammatory cytokine release

<table>
<thead>
<tr>
<th>Factor</th>
<th>Liver Disease</th>
<th>Vitamin K Def</th>
<th>DIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>V</td>
<td>↓</td>
<td>N</td>
<td>↓</td>
</tr>
<tr>
<td>VII</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>VIII</td>
<td>N/↑</td>
<td>N</td>
<td>↓</td>
</tr>
</tbody>
</table>
Table 27. Etiology of DIC

<table>
<thead>
<tr>
<th>Activation of Procoagulant Activity</th>
<th>Endothelial Injury</th>
<th>Reticuloendothelial Injury</th>
<th>Vascular Stasis</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiphospholipid antibody syndrome (APS)</td>
<td>Infections/sepsis</td>
<td>Liver disease</td>
<td>Hypotension</td>
<td>Acute hypercoagulability</td>
</tr>
<tr>
<td>Intravascular hemolysis</td>
<td>Vasculitis</td>
<td>Splenectomy</td>
<td>Hypovolemia</td>
<td>Extracorporeal circulation</td>
</tr>
<tr>
<td>Incompatible blood, malaria</td>
<td>Metastatic adenocarcinoma</td>
<td>Pulmonary embolus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tissue injury</td>
<td>Aortic aneurysm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obstetric complications, trauma, burns, crush injuries</td>
<td>Giant hemangioma</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Solid tumours, hematologic malignancies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(especially APLM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Snake venom, fat embolism, heat stroke</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- presence of both hemorrhage and clotting

Table 28. Clinical Features of DIC

<table>
<thead>
<tr>
<th>Signs of Microvascular Thrombosis</th>
<th>Signs of Hemorrhagic Diathesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurological: multifocal infarcts, delirium, coma, seizures</td>
<td>Bleeding from any site in the body (2° to decreased platelets and clotting factors)</td>
</tr>
<tr>
<td>Skin: focal ischemia, superficial gangrene</td>
<td>Neurologic: intracranial bleeding</td>
</tr>
<tr>
<td>Renal: oliguria, azotemia, cortical necrosis</td>
<td>Skin: petechiae, ecchymosis, oozing from puncture sites</td>
</tr>
<tr>
<td>Pulmonary: ARDS</td>
<td>Renal: hematuria</td>
</tr>
<tr>
<td>GI: acute ulceration</td>
<td>Mucosal: gingival oozing, epistaxis, massive bleeding</td>
</tr>
<tr>
<td>RBC: microangiopathic hemolysis</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
- primary hemostasis: decreased platelets
- secondary hemostasis: prolonged INR (PT), aPTT, TT, decreased fibrinogen and other factors
- fibrinolysis: increased FDPs or D-dimers, short euglobulin lysis time (i.e. accelerated fibrinolysis)
- extent of fibrin deposition: urine output, urea, RBC fragmentation

Treatment
- recognize early and treat underlying disorder
- individualized critical care support
- in hemorrhage: replacement of hemostatic elements with platelet transfusion, frozen plasma, cryoprecipitate
  - maintain platelets >50 x10^9, hemoglobin >80 g/L, calcium between 2.2-2.7 mmol/L, and avoid hypothermia
  - 4-5 units of FFP if INR >1.5 or aPTT >38
  - 10 units of cryoprecipitate if fibrinogen <1 g/L
  - 1 adult dose of buffy-coat platelets if <10 x10^9 (<20 if febrile, <50 before invasive procedure)
- in thrombotic phase: UFH or LMWH in critically ill, non-bleeding patients

Table 29. Screening Test Abnormalities in Coagulopathies

<table>
<thead>
<tr>
<th>Increased INR Only</th>
<th>Increased PTT Only</th>
<th>Both Increased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Warfarin</td>
<td>Homophilia A and B</td>
<td>Prothrombin deficiency</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>vWD</td>
<td>Fibrinogen deficiency</td>
</tr>
<tr>
<td>Factor VII deficiency</td>
<td>Heparin</td>
<td>Factor V and X deficiency</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Antiphospholipid Ab</td>
<td>Severe liver disease</td>
</tr>
<tr>
<td>Factor VII inhibitors</td>
<td>Factor inhibitors</td>
<td>Factor V and X, protrombin, and fibrinogen inhibitors</td>
</tr>
<tr>
<td>Factor XII and XII deficiency</td>
<td></td>
<td>Excessive anticoagulation</td>
</tr>
</tbody>
</table>

Hypercoagulable Disorders

Hypercoagulability Workup – Venous Thrombosis
- work up for malignancy is suggested in the event of abnormal blood work, constitutional symptoms or physical exam suggestive of cancer
- all patients should have age-appropriate cancer screening if not already done
- work up for hypercoagulable state is controversial and should only be done if it will alter treatment decisions
- recommendations for a hypercoagulable work up include:
  - heparin resistance (ATIII deficiency)
  - warfarin-induced skin necrosis or neonatal purpura fulminans (protein C or S deficiency)
  - consider for patients with a family history of VTE who are considering OCP use
  - consider for patients who present with thrombosis at an unusual venous site
- Arterial thrombotic events have only been proven to be associated with APLA, HIT, JAK2 MPNs, and PNH

American Society of Hematology

Choosing Wisely Recommendations
1. Do not test for thrombophilia in adult patients with venous thromboembolism occurring in the setting of major transient risk factors (surgery, trauma, or prolonged immobility)
2. Do not use inferior vena cava filters routinely in patients with acute venous thromboembolism
CAUSES OF HYPERCOAGULABILITY LEADING TO VENOUS THROMBOEMBOLISM

Activated Protein C Resistance (Factor V Leiden)
- most common cause of hereditary thrombophilia
- 3-7% of European Caucasian population are heterozygotes
- point mutation in the Factor V gene (R506Q) results in resistance to inactivation of Factor Va by activated protein C

Prothrombin Gene Mutation (PT) G20210A
- 1-3% of European Caucasian population are heterozygotes
- G to A transposition at nucleotide position 20210 of the prothrombin gene promoter region results in increased levels of prothrombin, thus increased thrombin generation

Protein C and Protein S Deficiency
- protein C inactivates Factor Va and VIIIa using protein S as a cofactor
- protein C deficiency
  - homozygous or compound heterozygous: neonatal purpura fulminans
  - heterozygous
    - type I: decreased protein C levels
    - type II: decreased protein C activity
  - acquired: liver disease, sepsis, DIC, warfarin, certain chemotherapeutic agents
- 1/3 of patients with warfarin necrosis have underlying protein C deficiency
- protein S deficiency
  - type I: decreased free and total protein S levels
  - type II: decreased protein S activity
  - type III: decreased free protein S levels
  - acquired: liver disease, DIC, pregnancy, nephrotic syndrome, inflammatory conditions, warfarin

Antithrombin Deficiency
- antithrombin slowly inactivates thrombin in the absence of heparin, rapidly inactivates thrombin in the presence of heparin
- autosomal dominant inheritance, urinary losses in nephrotic syndrome, or reduced synthesis in liver disease
- type I: decreased AT levels
- type II: decreased AT activity
- diagnosis must be made outside window of acute thrombosis and anticoagulation treatment (acute thrombosis, heparin, systemic disease all decrease antithrombin levels)
- deficiency may result in resistance to unfractionated heparin (LMWH may be considered, with monitoring of anti-Xa levels)

Elevated Factor VIII Levels
- an independent marker of increased incident and recurrent thrombotic risk, but levels can also be increased in numerous states as an acute phase reactant, therefore its clinical use is controversial
- genetic basis for increased levels poorly understood

Disorders of Fibrinolysis
- includes congenital plasminogen deficiency, tissue plasminogen activator deficiency, although association with VTE risk is not clear

Antiphospholipid Antibody Syndrome (APS)
- definition: ≥1 clinical and ≥1 laboratory criteria
- clinical: thrombosis, recurrent (>3) early pregnancy losses <10 weeks, one late fetal loss ≥10 weeks (morphologically normal), or premature birth before 34 wk due to (pre)eclampsia or placental insufficiency
- note: most of these tests do not change management, and a negative test does not rule out a hypercoagulable state
- thus more focus on the reversible/treatable causes (APLA, cancer, etc.)
Venous Thromboembolism

**Definition**
- thrombus formation and subsequent inflammatory response in a superficial or deep vein
- superficial thrombophlebitis, deep vein thrombosis (DVT), and pulmonary embolism (PE)
- thrombi propagate in the direction of blood flow (commonly originating in calf veins)
- more common in lower extremity than upper extremity
- incidence ~1% if age >60 yr
- most important sequelae are pulmonary embolism (~50% chance with proximal DVT) and chronic venous insufficiency

**Etiology (Virchow’s Triad)**
- endothelial damage
  - exposes endothelium to prompt hemostasis
  - leads to decreased inhibition of coagulation and local fibrinolysis
- venous stasis
  - immobilization (post-MI, CHF, stroke, post-operative) inhibits clearance and dilution of coagulation factors
- hypercoagulability
  - inherited (see *Hypercoagulable Disorders*, H33)
  - acquired
    - age (risk increases with age)
    - surgery (especially orthopedic, thoracic, GI, and GU)
    - trauma (especially fractures of spine, pelvis, femur or tibia, spinal cord injury)
    - neoplasms (especially lung, pancreas, colon, rectum, kidney, and prostate)
    - blood dyscrasias (myeloproliferative neoplasms, especially PV, ET), PNH, hyperviscosity (multiple myeloma, polycthemia, leukemia, sickle cell disease)
    - prolonged immobilization (CHF, stroke, MI, leg injury)
    - hormone related (pregnancy, OCP, HRT, SERMs)
    - APS
    - heart failure (risk of DVT greatest with right heart failure and peripheral edema)
  - idiopathic (10-20% are later found to have cancer)

**Clinical Features of DVT**
- absence of physical findings does not rule out disease
- unilateral leg edema, erythema, warmth, and tenderness
- palpable cord (thrombosed vein)
- phlegmasia alba dolens (white appearance) and phlegmasia cerula dolens (acute pain and edema) with massive thrombosis
- Homan’s sign (pain with foot dorsiflexion) is unreliable

**Differential Diagnosis of DVT**
- muscle strain or tear, lymphangitis or lymph obstruction, venous valvar insufficiency, ruptured popliteal cysts, cellulitis, arterial occlusive disease

**Investigations for DVT**
- D-dimer test only useful to rule out DVT if negative with low clinical suspicion of disease and no other acute medical issues
- doppler ultrasound is most useful diagnostic test for DVT
  - sensitivity and specificity for proximal DVT ~95%
  - sensitivity for calf DVT ~70%
- other non-invasive tests include MRI and impedance plethysmography
- venography is the gold standard, but is expensive, invasive, and higher risk

**Post-Thrombotic Syndrome**
- development of chronic venous stasis signs and symptoms secondary to a deep venous thrombosis
- symptoms: pain, venous dilatation, edema, pigmentation, skin changes, venous ulcers
- clinical severity can be estimated based on the Villalta score
- large impact on quality of life following a DVT treatment: extremity elevation, exercise, continuous compression stockings, intermittent pneumatic compression therapy, skin/ulcer care
- for Clinical Features and Treatment of PE, see *Respirology*, R18

**Risk of VTE in Hospitalized Patients Receiving Ineffective Antithrombotic Therapy**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>RR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;75 yr</td>
<td>1.79 (1.18-2.71)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.50 (1.01-2.51)</td>
<td>0.03</td>
</tr>
<tr>
<td>Previous VTE</td>
<td>1.67 (1.01-2.77)</td>
<td>0.08</td>
</tr>
<tr>
<td>Obesity</td>
<td>0.94 (0.59-1.51)</td>
<td>0.91</td>
</tr>
<tr>
<td>Hormone therapy</td>
<td>0.51 (0.08-3.38)</td>
<td>0.70</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1.00 (0.72-1.62)</td>
<td>0.92</td>
</tr>
<tr>
<td>NYHA III</td>
<td>0.91 (0.55-1.43)</td>
<td>0.72</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>1.46 (0.84-2.6)</td>
<td>0.27</td>
</tr>
<tr>
<td>Acute infectious disease</td>
<td>1.50 (1.00-2.26)</td>
<td>0.06</td>
</tr>
<tr>
<td>Acute respiratory disease</td>
<td>1.45 (0.94-2.59)</td>
<td>0.27</td>
</tr>
</tbody>
</table>

**Source:** JAMA 2006;164:963-968

**Wells’ Score for DVT**

<table>
<thead>
<tr>
<th>Criteria (Score)</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paralysis</td>
<td>1</td>
</tr>
<tr>
<td>Paresis</td>
<td>1</td>
</tr>
<tr>
<td>Recent surgery</td>
<td>1</td>
</tr>
<tr>
<td>Acute venous occlusion</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Recovery time</td>
<td>1</td>
</tr>
<tr>
<td>Localized tenderness in deep vein system</td>
<td>1</td>
</tr>
<tr>
<td>Swelling of entire leg</td>
<td>1</td>
</tr>
<tr>
<td>Calf swelling &gt;3 cm than other leg (measured 10 cm below the tibial tuberosity)</td>
<td>1</td>
</tr>
<tr>
<td>Pitting edema greater in the symptomatic leg</td>
<td>1</td>
</tr>
<tr>
<td>Collateral non-varicose superficial veins</td>
<td>1</td>
</tr>
<tr>
<td>Active cancer or cancer treated within 6 mo</td>
<td>1</td>
</tr>
<tr>
<td>Alternative diagnosis more likely than DVT (e.g. Baker’s cyst, cellulitis, muscle damage, superficial venous thrombosis)</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total Score Interpretation**
- 3-8: High probability, 1-2: Moderate probability, 0-2: Low probability

**Low-Molecular-Weight Heparin vs. Coumarin for the Prevention of Recurrent Venous Thromboembolism in Patients with Cancer**

<table>
<thead>
<tr>
<th>Study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT comparing the efficacy of LMWH (dalteparin) in preventing recurrent thrombosis in patients with cancer.</td>
<td>Patients with cancer who had acute, symptomatic proximal DVT, PE, or both were randomly assigned to either dalteparin or coumarin treatment for 6 mo.</td>
</tr>
<tr>
<td>Dalteparin group and 41% in the coumarin group.</td>
<td>The mortality rate was 39% in the dalteparin group and 41% in the coumarin group.</td>
</tr>
</tbody>
</table>
| Dalteparin was more effective than coumarin in decreasing the risk of recurrent thromboembolism without increasing the risk of bleeding. |}

**Vital Signs**

- temperature (oral or axillary)
- heart rate
- respiratory rate
- blood pressure
- oxygen saturation

**Summary**
- Thromboembolism is a common and serious complication of cancer, with a prevalence of 22% in patients with cancer and a lifetime risk of 30%.
- Early recognition and appropriate management are crucial to minimize morbidity and mortality.
- Antithrombotic therapy is the cornerstone of prophylaxis and treatment.
- Monitoring of laboratory markers, such as D-dimer, is crucial for guiding therapy.
- Regular assessment of clinical symptoms and physical examination is necessary to detect and treat post-thrombotic syndrome.

**Conclusion**
- Thromboembolism is a significant complication of cancer, and effective management requires a multidisciplinary approach.
- Early recognition and timely intervention can improve outcomes and quality of life for patients with cancer.
Approach to Treatment of Venous Thromboembolism

**Purpose**
- prevent further clot extension (3 mo duration is optimal)
- prevent acute pulmonary embolism (occurs in up to 50% of untreated patients)
- reduce the risk of recurrent thrombosis (duration depends on presence of other risk factors)
- treatment of massive iliofemoral thrombosis with acute lower limb ischemia and/or venous gangrene (phlegmasia cerulea dolens)
- limit development of late complications (e.g. postphlebitic syndrome, chronic venous insufficiency, and chronic thromboembolic pulmonary HTN)

**Initial Treatment**
- low molecular weight heparin (LMWH)
  - administered SC, at least as effective as UFH with a lower bleeding risk
  - advantages: predictable dose response and fixed dosing schedule; lab monitoring not required; <1% HIT; safe and effective outpatient therapy
  - disadvantages: only partially reversible by protamine, long-term use associated with osteoporosis
  - renalally cleared – must adjust dose in patients with renal dysfunction
- unfractionated heparin (UFH)
  - in patient with average risk of bleed; use hospital-based nomograms that use bleeding risk and patient weight to determine appropriate dose
  - advantages: rapidly reversible by protamine
  - disadvantages: must monitor aPTT or heparin levels with adjustment of dose to reach therapeutic level (~2x normal value); monitor platelet counts for development of HIT
- alternatives to LMWH and UFH
  - direct thrombin inhibitors (hirudin, lepirudin, argatroban), Factor Xa inhibitors (fondaparinux, rivaroxaban)
  - thrombolytic drugs (e.g. streptokinase, tPA) reserved for acute limb/life-threatening thrombosis, and low bleeding risk

**Long-Term Treatment**
- warfarin
  - standard treatment; should be initiated with heparin overlap: dual therapy for at least 5 d, due to initial prothrombotic state, half life of vitamin K factors and risk of warfarin-induced skin necrosis
  - discontinue heparin after INR >2.0 for 2 consecutive days
  - warfarin should be dosed to maintain INR at 2-3 except in select cases
  - monitor INR twice weekly for 1-2 wk, then weekly until INR stable, then every 2-4 wk
  - LMWH more effective than warfarin at preventing recurrence of venous thrombosis in cancer patients (see sidebar, H35)
  - duration of anticoagulant treatment (with warfarin unless otherwise noted)
    - first episode DVT with transient risk factor: 3 mo
    - first episode DVT with ongoing risk factor (e.g. immobility, antiphospholipid antibody) or >1 risk factor: consider indefinite therapy
    - cancer-associated DVT: prefer LMWH over warfarin for duration of cancer therapy or for as long as cancer remains active
    - first episode DVT with no identifiable risk factor (idiopathic) or single inherited risk factor (e.g. Factor V Leiden): 6-12 mo or indefinite therapy if bleeding risk low
    - recurrent DVT (2 or more episodes): indefinite therapy
- IVC filters
  - temporary filter indicated only if acute DVT (<4 wk) with significant contraindications to anticoagulant therapy (i.e. active bleeding) or if require interruption of anticoagulation (i.e. for surgery)
  - must be retrieved once safe to do so as filter is pro-thrombotic in the long-term (consider anticoagulation if not retrieved)
- special considerations
  - pregnancy: treat with LMWH during pregnancy, then LMWH or warfarin for 6 wk post-partum (minimum total anticoagulation time of 3-6 mo, but must include 6 ws post-partum, as this is a high risk period)
  - surgery: avoid elective surgery in the first month after a venous or arterial thromboembolic event
    - pre-operatively: IV heparin may be used up to 6 h pre-operatively
    - perioperatively: surgery safe when INR <1.5; warfarin should be discontinued for at least 5 d pre-operatively to allow INR to fall
    - post-operatively: IV heparin or LMWH can be used for anticoagulation (start 12 h after major surgery until therapeutic INR reached after restarting warfarin)
    - for patients at high risk for thromboembolism (VTE <12 wk, recurrent VTE, lupus anticoagulant, atrial fibrillation with prior stroke, mechanical heart valve), IV heparin or LMWH (bridging) should be given before and after the procedure while the INR is below 2.0

---

**Duration of Treatment with Vitamin K Antagonists in Symptomatic Venous Thromboembolism**

*Study: Meta-analysis of 8 RCTs (2,994 patients)*

*Comparing different durations of treatment with vitamin K antagonists in patients with symptomatic VTE.*

*Results: In patients treated with vitamin K antagonists for a prolonged period, the reduction in risk of recurrent VTE remained consistent regardless of the period of time since the index event (OR 0.18; 95%CI 0.13-0.25). In addition, there was no observed excess of VTE recurrences following cessation of prolonged treatment (i.e. rebound phenomenon) (OR 1.24; 95%CI 0.91-1.69). However, patients who received prolonged treatment had a persistent increase in their risk of major bleeding complications (OR 2.61; 95%CI 1.40-4.67).*

*Conclusion: Prolonged treatment with vitamin K antagonists leads to a consistent reduction in the risk of recurrent VTE for as long as therapy is continued. Therapy should be discontinued when the risk of harm from major bleeding (which remains constant over time) is of greater concern than the absolute risk of recurrent VTE (which declines over time). No specific recommendation was made regarding optimal duration of treatment.*

**Common Medications that Interact with Warfarin**

- Acetaminophen (interference with vitamin K metabolism)
- Allopurinol
- NSAIDs (GI injury)
- Fluconazole
- Metronidazole
- Sulfamethoxazole
- Tamoxifen

**Initiation of Warfarin Therapy Requires Bridging with Heparin Therapy for 4-5 Days**

- 10 mg loading dose of warfarin causes a precipitous decline in protein C levels in first 36 h resulting in a transient hypercoagulable state
- Warfarin decreases Factor VII levels in first 48 h, INR is prolonged (most sensitive to Factor VII levels), however full antithrombotic effect is not achieved until Factor IX, X, and II are sufficiently reduced (occurs after ~6 d)

**Low Risk Surgical Patients**

<40 yr, no risk factors for VTE, general anesthetic (GA) <30 min, minor elective, abdominal, or thoracic surgery

**Moderate Risk Surgical Patients**

>40 yr, >1 risk factor for VTE, GA >30 min

**High Risk Surgical Patients**

>40 yr, surgery for malignancy or lower extremity orthopedic surgery lasting >30 min, inhibitor deficiency, or other risk factor

**High Risk Medical Patients**

Heart failure, severe respiratory disease, ischemic stroke and lower limb paralysis, confined to bed and have >1 additional risk factor (e.g. active cancer, previous VTE, sepsis, acute neurologic disease, IBD)
**Prophylaxis**
- see sidebar
- consider for those with a moderate to high risk of thrombosis without contraindications
- non-pharmacological measures include: early ambulation, elastic compression stockings (TEDs), intermittent pneumatic compression (IPC)
- UFH 5,000 IU SC bid for moderate risk
- UFH 5,000 IU SC tid or LMWH as per hospital protocol (i.e. enoxaparin 40 mg SC daily) or UFH 5,000 IU SC tid for high risk

**Contraindications and Adverse Reactions of Anticoagulant Therapy**
- absolute: active bleeding, severe bleeding diathesis, or platelets <20 x 10⁹/L (<20,000/mm³), intracranial bleeding, neuro or ocular surgery within <10 d
- relative: mild-moderate neurologic diathesis or thrombocytopenia, brain metastases, recent major trauma, major abdominal surgery within past 2 d, GI/GU bleed within 14 d, endocarditis, severe HTN (sBP >200 or dBP >120), recent stroke

**Table 30. Contraindications of Anticoagulant Therapy**

<table>
<thead>
<tr>
<th>Active bleeding</th>
<th>Severe bleeding diathesis or platelet count &lt;20 x 10⁹/L (&lt;20,000/mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial bleeding</td>
<td>Neurosurgery or ocular surgery within 10 d</td>
</tr>
<tr>
<td>Mild-moderate bleeding diathesis or thrombocytopenia</td>
<td>Brain metastases</td>
</tr>
<tr>
<td>Recent major trauma</td>
<td>Recent stroke</td>
</tr>
<tr>
<td>Major abdominal surgery within past 2 d</td>
<td>GI/GU bleeding within 1-4 d</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>Severe hypertension (sBP &gt;200 or dBP &gt;120)</td>
</tr>
</tbody>
</table>

**Treatment of Pulmonary Embolism**
- see Respiniology, R18

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**Hemotechn Malignancies and Related Disorders**

**Figure 14. Overview of hematologic malignancies and related disorders**

**Myeloid Malignancies**

**Acute Myeloid Leukemia**

**Definition**
- rapidly progressive malignancy characterized by failure of myeloid cells to differentiate beyond blast stage

**Epidemiology**
- incidence increases with age; median age of onset is 65 yr old
- accounts for 10-15% of childhood leukemias

**Risk Factors**
- myelodysplastic syndromes (MDS), benzene, radiation, Down Syndrome, alkylating agents as treatment for previous malignancy
Pathophysiology
- etiology subdivided into
  - primary: de novo
  - secondary: hematologic malignancies (e.g. myeloproliferative disorders and MDS) or previous chemotherapeutic agents (e.g. alkylating agents)
- uncontrolled growth of blasts in marrow leads to
  - suppression of normal hematopoietic cells
  - appearance of blasts in peripheral blood
  - accumulation of blasts in other sites (e.g. skin, gums)
  - metabolic consequences; tumour lysis syndrome

Clinical Features
- anemia, thrombocytopenia (associated with DIC in promyelocytic leukemia), neutropenia (even with normal WBC), leads to infections, fever
- accumulation of blast cells in marrow
  - skeletal pain, bony tenderness (especially sternum)
- organ infiltration
  - gingival hypertrophy (particularly myelomonocytic leukemia) – may present to dentist first
  - hepatosplenomegaly (in ALL)
  - lymphadenopathy (not marked in ALL)
  - gonads (in ALL)
  - skin: leukemia cutis
  - eyes: Roth spots, cotton wool spots, vision changes (uncommon)
- leukostasis/hyperleukocytosis syndrome (medical emergency)
  - large numbers of blasts interfere with circulation and lead to hypoxia and hemorrhage – can cause diffuse pulmonary infiltrates, CNS bleeding, respiratory distress, altered mental status, priapism
  - associated with AML more than ALL
- metabolic effects; aggravated by treatment (rare)
  - increased uric acid → nephropathy, gout
  - release of phosphate → decreased Ca²⁺, decreased Mg²⁺
  - release of procoagulants → DIC (higher risk in acute promyelocytic leukemia)
  - decreased or normal K⁺ before treatment, increased K⁺ after treatment (from lysed cells)

Investigations
- blood work
  - CBC: anemia, thrombocytopenia, variable WBC
  - INR, aPTT, fibrin degradation products (FDP), fibrinogen (in case of DIC)
  - increased LDH, increased uric acid, increased PO₄³⁻ (released by leukemic blasts), decreased Ca²⁺, decreased K⁺
  - baseline renal and liver function tests
- peripheral blood film – circulating blasts with Auer rods (azurophilic granules) are pathognomonic for AML
- bone marrow aspirate
  - blast count: AML >20% (normal is <5%)
  - morphologic, cytochemical, and/or immunotypic features are used to establish lineage and maturation (see sidebar for WHO classification of AML, H37)
- CXR to rule out pneumonia, ECG, MUGA scan prior to chemotherapy (cardiotoxic)

Treatment
- mainstay of treatment is chemotherapy (rapidly fatal without treatment)
  - all AML subtypes are treated similarly, except acute promyelocytic leukemia (APL) with t(15:17) translocation
    - all-trans-retinoic acid (ATRA) added to induce differentiation; arsenic trioxide + ATRA combination therapy for APL is non-inferior to traditional chemotherapy
  - treatment strategy
    1. Induction: chemotherapy to induce complete remission of AML (see sidebar)
      - several possible regimens (e.g. cytarabine with anthracycline [daunorubicin])
      - patients with poor response to initial induction therapy – worse prognosis
      - must ensure reversal of DIC, platelet transfusions if <10
    2. Consolidation: to prevent recurrence
      - intensive consolidation chemotherapy
      - stem cell transplantation – autologous or allogeneic (younger patients with better performance status)
  - consider acceleration with hematopoietic growth factors (e.g. G-CSF) if severe infection develops
  - supportive care
    - screening for infection via regular C&S of urine, stool, sputum, oropharynx, catheter sites, perianal area
    - fever: C&S of all orifices, CXR, start antibiotics
    - platelet and RBC transfusions (irradiated to prevent transfusion-related GVHD) ± EPO
    - prevention and treatment of metabolic abnormalities
      - allopurinol, rasburicase for prevention of hyperuricemia
Prognosis
- achievement of first remission
  - 70-80% if ≤60 yr old, 50% if >60 yr old median survival 12-24 mo
  - 5 yr survival 40%
  - prognosis is most related to cytogenetics; classified as favourable, intermediate, or adverse

Myelodysplastic Syndromes

Definition
- heterogeneous group of malignant stem cell disorders characterized by dysplastic and ineffective blood cell production resulting in peripheral cytopenias
- syndromes defined according to World Health Organization (WHO) classifications

Pathophysiology
- disordered maturation: ineffective hematopoiesis despite presence of adequate numbers of progenitor cells in bone marrow (usually hypercellular)
- both processes lead to reduced mature cells in periphery
- <30% develop AML

Risk Factors
- elderly, post-chemotherapy, benzene or radiation exposure
- occurs in 4/100,000 patients >60 yr old

Clinical Features
- insidious onset: associated with pancytopenia
- infections and bleeding out of proportion with peripheral blood counts

Investigations
- diagnosed by
  - anemia ± thrombocytopenia ± neutropenia
  - CBC and peripheral blood film
  - RBC: usually macrocytic with oval shaped red cells (macro-ovalocytes), decreased reticulocyte count
  - WBC: decreased granulocytes and abnormal morphology (e.g. bilobed or unsegmented nuclei = Pelger abnormality)
  - platelets: thrombocytopenia, abnormalities of size and cytoplasm (e.g. giant hypogranular platelets)
- bone marrow aspirate and biopsy with cytogenetic analysis required for definitive diagnosis
- bone marrow: dysplastic and often normocellular/hypercellular
- cytogenetics: partial or total loss of chromosomes 5, 7, Y, or trisomy 8

Treatment
- low risk of transformation to acute leukemia (IPSS-R Very Low or Low)
  - erythropoietin stimulating agents weekly is first line in reducing transfusion requirements
  - If 5q deletion based on cytogenics: lenalidomide PO supportive care: RBC and platelet transfusion (consider iron chelation if frequent RBC transfusions)
- high risk of transformation to acute leukemia (IPSS-R Intermediate, High or Very High)
  - supportive care
  - stem cell transplantation if age <65 yr
  - epigenetic therapy: DNA methyltransferase inhibitors (e.g. 5-azacytidine), histone deacetylase inhibitors

Prognosis
- Revised International Prognostic Scoring System (IPSS-R) uses 5 factors to estimate mean survival
  - cytology, % bone marrow blasts, hemoglobin, platelets, absolute neutrophil count
  - based on the calculated score, a patient's MDS prognostic risk is "Very Low", "Low", "Intermediate", "High", or "Very High" with a mean survival of 8.7, 5.3, 3.0, 1.6, and 0.8 yr, respectively

Myeloproliferative Neoplasms

Definition
- clonal myeloid stem cell abnormalities leading to overproduction of one or more cell lines (leading to abnormalities in erythrocytes, platelets, and other cells of myeloid lineage)

Epidemiology
- mainly middle-aged and older patients (peak 60-80 yr)
**Prognosis**
- may develop marrow fibrosis with time
- all disorders may progress to AML

**Table 31. Chronic Myeloproliferative Disorders**

<table>
<thead>
<tr>
<th></th>
<th>CML</th>
<th>PV</th>
<th>IMF</th>
<th>ET</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hct</td>
<td>↓/N</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
</tr>
<tr>
<td>WBC</td>
<td>↑</td>
<td>↑</td>
<td>↑/↓</td>
<td>N</td>
</tr>
<tr>
<td>Plt</td>
<td>↑/↓</td>
<td>↑</td>
<td>↓/↓</td>
<td>↑</td>
</tr>
<tr>
<td>Marrow Fibrosis</td>
<td>±</td>
<td>±</td>
<td>+++</td>
<td>±</td>
</tr>
<tr>
<td>Splenomegaly</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Hepatomegaly</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Genetic Association</td>
<td>bcr-abl mut. (90+%); JAK2 mut. (96%); JAK2 mut. (~50%); JAK2 mut. (~50%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CML = chronic myeloid leukemia; ET = essential thrombocythemia; IMF = idiopathic myelofibrosis; PV = polycythemia vera

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**Chronic Myeloid Leukemia**

**Definition**
- myeloproliferative disorder characterized by increased proliferation of the granulocytic cell line without the loss of their capacity to differentiate

**Epidemiology**
- occurs in any age group (mostly middle age to elderly) with a median age of 65 yr

**Pathophysiology**
- Philadelphia chromosome (Ph)
  - translocation between chromosomes 9 and 22
  - the c-abl proto-oncogene is translocated from chromosome 9 to “breakpoint cluster region” (bcr) of chromosome 22 to produce bcr-abl fusion gene, an active tyrosine kinase

**Clinical Features**
- 3 clinical phases
  - chronic phase: 85% diagnosed here
    - few blasts (<10%) in peripheral film
    - ± slightly elevated eosinophils and basophils
    - no significant symptoms
  - accelerated phase: impaired neutrophil differentiation
    - circulating blasts (10-19%) with increasing peripheral basophils (pruritus)
    - CBC: thrombocytopenia <100 x 10^9/L
    - cytogenetic evidence of clonal evolution
    - worsening constitutional symptoms and splenomegaly (extramedullary hematopoiesis)
  - blast crisis: more aggressive course, blasts fail to differentiate
    - blasts (>20%) in peripheral blood or bone marrow; reflective of acute leukemia (1/3 ALL, 2/3 AML)
    - clinical presentation
      - 20-50% of patients are asymptomatic when diagnosed (incidental lab finding)
      - nonspecific symptoms
        - fatigue, weight loss, malaise, excessive sweating, fever
      - secondary to splenic involvement
        - early satiety, LUQ pain/fullness, shoulder tip pain (referred)
      - splenomegaly (most common physical finding)
      - anemia
      - bleeding: secondary to platelet dysfunction
      - pruritus, PUD: secondary to increased blood histamine
      - leukostasis, priapism, encephalopathy (rare): secondary to very elevated WBC (rare)

**Investigations**
- elevated WBC, decreased/normal RBC, increased/decreased platelets, increased basophils
- WBC differential shows a bimodal distribution, with predominance of myelocytes and neutrophils
- peripheral blood film
  - leukoerythroblastic picture (immature red cells and granulocytes present, e.g. myelocytes and normoblasts)
  - presence of different mid-stage progenitor cells differentiates it from AML
- bone marrow
  - myeloid hyperplasia with left shift, increased megakaryocytes, mild fibrosis
  - molecular and cytogenetic studies of bone marrow or peripheral blood for Philadelphia chromosome
- abdominal imaging for spleen size

---

**Chronic Myeloproliferative Neoplasms: Six Year Follow-Up of Patients Receiving Imatinib for the First-Line Treatment of CML**

**Study**
- The Randomized Study of Interferon vs. STI571 (IRIS) trial enrolled patients with chronic phase chronic myeloid leukemia (CML-CP) to either imatinib (n=533) or interferon-α (IFN) plus cytarabine (n=553).

**Results**
- Assessing the imatinib arm specifically at the sixth year point, there were no reports of disease progression to accelerated phase (AP) or blast crisis (BC), toxicity profile was unchanged, and cytogenetic response rate was 82%. Estimated event-free survival was 83% and rate of freedom from progression to AP and BC was 93%.

**Conclusion**
- This 6-year update of IRIS demonstrates the efficacy and safety of imatinib as first-line therapy for CML patients.

Basophilia is uncommon in other medical conditions
Treatment

• symptomatic
  ▪ allopurinol and antihistamines

• chronic phase
  ▪ imatinib mesylate inhibits proliferation and induces apoptosis by inhibiting tyrosine kinase activity in cells positive for bcr-abl
    • if loss of response or intolerance (~25%), trial of 2nd (dasatinib) or 3rd (nilotinib) generation inhibitors
    • dasatinib and nilotinib may also be considered for first line management
  ▪ interferon-α: may improve response to tyrosine kinase inhibitors; typically now only used for pregnant patients
  ▪ hydroxyurea in palliative setting to reduce WBC

• accelerated phase or blast phase
  ▪ refer for clinical trial or 2nd/3rd generation TKI and prepare for allogeneic stem cell transplant patients, in blast phase typically get standard AML induction
  ▪ stem cell transplantation may be curative: to be considered in young patients who do not meet therapeutic milestones
  ▪ treatment success is monitored based on therapeutic milestones
    ▪ hematologic: improved WBC and platelet counts, reduced basophils
    ▪ cytogenetic: undetectable Philadelphia-chromosome in the bone marrow
    ▪ molecular: reduction/absence of bcr-abl transcripts in periphery and marrow

Prognosis

• survival dependent on response
  ▪ those achieving complete cytogenetic response (CCR) on imatinib by 18 mo of therapy: 6 yr overall survival >90%
  ▪ those who do NOT achieve CCR on imatinib: 6 yr overall survival of 66%
  ▪ acute phase (blast crisis – usually within 3-5 yr)
    ▪ 2/3 develop a picture similar to AML
    ▪ unresponsive to remission induction
  ▪ 1/3 develop a picture similar to ALL
    ▪ remission induction (return to chronic phase) achievable

Polycythemia Vera

Definition

• stem cell disorder characterized by elevated RBC mass (erythrocytosis) ± increased white cell and platelet production

Clinical Features

• symptoms are secondary to high red cell mass and hyperviscosity (see Erythrocytosis, H6)
  ▪ bleeding complications: epistaxis, gingival bleeding, ecchymoses, and GI bleeding
    ▪ due to platelet abnormalities
  ▪ thrombotic complications: DVT, PE, thrombophlebitis, increased incidence of stroke, MI
    ▪ due to increased blood viscosity, increased platelet number and/or activity
  ▪ erythromelalgia (burning pain in hands and feet and erythema of the skin)
    ▪ associated with platelets >400 x 10^9/L
    ▪ pathognomonic microvascular thrombotic complication in PV and ET
  ▪ pruritus, especially after warm bath or shower (40%)
    ▪ due to cutaneous mast cell degranulation and histamine release
  ▪ epigastric distress, PUD
    ▪ due to increased histamine from tissue basophils, alterations in gastric mucosal blood flow due to increased blood viscosity
  ▪ gout (hyperuricemia)
    ▪ due to increased cell turnover
  ▪ characteristic physical findings
    ▪ plethora (ruddy complexion) of face (70%), palms splenomegaly (70%), hepatomegaly (40%)

Investigations

• see Erythrocytosis, H6
  ▪ must rule out secondary polycythemia
  ▪ diagnosis (WHO 2008) requires either both major criteria plus one minor criteria OR the first major criterion plus 2 minor criteria
    ▪ Major Criteria
      1. hemoglobin >185 g/L in men, >165 g/L in women or other evidence of increased red cell volume
      2. presence of JAK2 V617F or other functionally similar mutation such as JAK2 exon 12 mutation
Minor Criteria
1. bone marrow biopsy showing hypercellularity for age with trilineage growth (panmyelosis) with prominent erythroid, granulocytic, and megakaryocytic proliferation
2. serum erythropoietin level below the reference range for normal
3. endogenous erythroid colony formation in vitro

Treatment
- phlebotomy to keep hematocrit <45%
- hydroxyurea (prior thrombosis or symptoms, severe coronary artery disease, refractory to phlebotomy)
- low-dose Aspirin® (for antithrombotic prophylaxis, will also treat erythromelalgia)
- allopurinol: as needed
- antihistamines: as needed

Prognosis
- 10-20 yr survival with treatment
- complicated by thrombosis, hemorrhage, leukemic transformation (AML)

Idiopathic Myelofibrosis

Definition
- excessive bone marrow fibrosis leading to marrow failure
- characterized by anemia, extramedullary hematopoiesis, leukoerythroblastosis, teardrop red cells in peripheral blood and hepatosplenomegaly

Epidemiology
- rare, median age at presentation is 65 yr

Pathophysiology
- abnormal myeloid precursor postulated to produce dysplastic megakaryocytes that secrete fibroblast growth factors
  - stimulates fibroblasts and stroma to deposit collagen in marrow
- increasing fibrosis causes early release of hematopoietic precursors leading to:
  - leukoerythroblastic blood film (primitive RBCs and WBCs present in blood)
  - migration of precursors to other sites: extramedullary hematopoiesis (leading to hepatosplenomegaly)

Clinical Features
- anemia (severe fatigue is most common presenting complaint, pallor on exam in >60%)
- weight loss, fever, night sweats → secondary to hypermetabolic state
- splenomegaly (90%) → secondary to extramedullary hematopoiesis; may cause early satiety
- hepatomegaly (70%) → may get portal hypertension
- bone and joint pain → secondary to osteosclerosis, gout
- signs of extramedullary hematopoiesis (depends on organ involved)

Investigations
- CBC: anemia, variable platelets, variable WBC
- biochemistry: increased ALP (liver involvement, bone disease), increased LDH (2° to ineffective hematopoiesis), increased uric acid (increased cell turnover), increased B12 (2° to increased neutrophil mass)
- blood film: leukoerythroblastosis with teardrop RBCs, nucleated RBCs, variable polychromasia, large platelets, and megakaryocyte fragments
- JAK2 PCR and calreticulin PCR
- bone marrow aspirate: “dry tap” in as many as 50% of patients (no blood cells aspirated)
- bone marrow biopsy (essential for diagnosis): fibrosis, atypical megakaryocytic hyperplasia, thickening and distortion of the bony trabeculae (osteosclerosis)

Treatment
- allogeneic stem cell transplant is potentially curative
- JAK2 inhibitors
- symptomatic treatment
  - transfusion for anemia
  - erythropoietin: 30-50% of patients respond
  - androgens for anemia (e.g. danazol has shown transient response with response rates of <30%)
  - hydroxyurea for splenomegaly, thrombocytosis, leukocytosis, systemic symptoms
    - interferon-α (as second line therapy)
  - splenectomy (as third line therapy; associated with high mortality and morbidity)
  - radiation therapy for symptomatic extramedullary hematopoiesis, symptomatic splenomegaly
  - thalidomide, and etanercept may improve quality of life and spleen size, but not survival

Efficacy and Safety of Low-dose Aspirin® in Polycythemia Vera
NEJM 2004;350:114-124
Study: Double-blind, placebo-controlled, RCT
Participants: 518 patients with polycythemia vera (PV) with no clear indication for, or contraindication to, ASA therapy.
Intervention: Patients received either low-dose ASA 100 mg daily (n=253) or placebo (n=265) and were followed for up to 5 yr.
Primary Outcome: Cumulative rate of (I) nonfatal MI, nonfatal stroke, or death from cardiovascular causes and the cumulative rate of (II) the previous 3 plus FE and major venous thrombosis.
Results: Primary outcomes (I) and (II) were reduced with treatment compared to placebo (RR 0.41; p=0.09 and RR 0.4; p=0.03, respectively). There were no differences in overall or cardiovascular mortality and major bleeding episodes.
Conclusion: Low-dose ASA can safely prevent thrombotic complications in patients with PV.

Myelofibrosis can be either primary (idiopathic) or occur as a transformation of an antecedent PV or ET

An “leukoerythroblastic” blood film (RBC and granulocyte precursors) implies bone marrow infiltration with malignancy (e.g. leukemias, solid tumour metastases) or fibrosis (e.g. IMF)

IMF typically has a dry BM aspirate and teardrop RBCs (aspiration gives no blood cells)

A Double-Blind, Placebo-Controlled Trial of Ruxolitinib for Myelofibrosis
NEJM 2012;366:799-807
Study: Double-blind RCT of 309 patients with myelofibrosis randomized to ruxolitinib or placebo.
Outcome: Primary outcome was reduction in spleen volume of >35% at 24 wk. Secondary outcomes were durability of response, symptom burden, and overall survival.
Results: A greater proportion of patients on ruxolitinib had reduction in spleen volume >35% (41.9% vs. 5.7%) and this was sustained in 67% at 48 wk. Ruxolitinib also led to greater symptom improvement (45% vs. 5.3%) and less mortality (13 vs. 24). There was no difference in rate of discrimination due to adverse events (11.2% vs. 10.8%) but anemia and thrombocytopenia were more common with ruxolitinib.
Conclusions: Ruxolitinib reduced spleen size, improved symptoms and improved survival, compared with placebo.
Prognosis
- International Prognostic Scoring System (IPSS) for IMF uses 5 factors to determine mean survival
  - presence of constitutional symptoms; age >65; hemoglobin <100 g/L; leukocyte count >25,000/mm³; circulating blast cells ≥1%
  - based on the calculated score, a patient’s IMF is categorized as “low”, “intermediate 1”, “intermediate 2”, or “high” with a mean survival of 135, 95, 48, and 27 mo respectively
- risk of transformation to AML (8-10%)

Essential Thrombocytopenia

Definition
- overproduction of platelets in the absence of recognizable stimulus
- must rule out secondary thrombocytopenia

Epidemiology
- increases with age; F:M = 2:1, but F=M at older age

Diagnosis (2008 WHO Criteria) requires meeting all four criteria:
1. sustained platelet count >450 x 10⁹/L
2. bone marrow biopsy specimen showing proliferation mainly of the megakaryocytic lineage with increased number of enlarged, mature megakaryocytes; no significant increase or left shift of neutrophil granulopoiesis or erythropoiesis
3. not meeting WHO criteria for PV, primary myelofibrosis, bcr-abl CML, or myelodysplastic syndrome or other myeloid neoplasms
4. demonstration of JAK2 V617F or calreticulin (or in its absence another clonal marker), no evidence for reactive thrombocytosis

Clinical Features
- often asymptomatic
- vasomotor symptoms (40%)
  - headache (common), dizziness, syncope
  - erythromelalgia (burning pain of hands and feet, dusky colour, usually worse with heat, caused by platelet activation → microvascular thrombosis)
- thrombosis (arterial and venous)
- bleeding (often GI; associated with platelets >1,000 x 10⁹/L)
- constitutional symptoms, splenomegaly
- pregnancy complications: increased risk of spontaneous abortion
- risk of transformation to AML (0.6-5%), myelofibrosis

Investigations
- CBC: increased platelets; may have abnormal platelet aggregation studies
- JAK2 PCR assay
- bone marrow hypercellularity, megakaryocytic hyperplasia, giant megakaryocytes
- increased K⁺, increased PO₄³⁻ (2⁻ to release of platelet cytoplasmic contents)
- diagnosis: exclude other myeloproliferative disorders and reactive thrombocytosis

Treatment
- low dose ASA if previous history of thrombotic event, ≥1 cardiovascular risk factors, older, or symptomatic
- cytotherapeutic therapy if thrombosis or thrombotic symptoms: hydroxyurea (HU) (1st line therapy), anagrelide, interferon-α, or 3²P (age >80 or lifespan <10 yr)
- splenectomy not recommended (increased risk of bleeding episodes, thrombosis)

Lymphoid Malignancies

Acute Lymphoblastic Leukemia

Definition
- malignant disease of the bone marrow in which early lymphoid precursors proliferate and replace the normal hematopoietic cells of the marrow
- WHO subdivides ALL into two types depending on cell of origin
  1. B-cell: precursor B lymphoblastic leukemia
  2. T-cell: precursor T lymphoblastic leukemia
- the French-American-British (FAB) classification (L1, L2, L3) is no longer encouraged, as morphology is not prognostic

75% of ALL occurs in children <6 yr old; second peak at age 40
Clinical Features
- see Acute Myeloid Leukemia, H37 for full list of symptoms
- distinguish ALL from AML based on Table 32
- clinical symptoms usually secondary to:
  - bone marrow failure: anemia, neutropenia (50% present with fever; also infections of oropharynx, lungs, perianal region), thrombocytopenia
  - organ infiltration: tender bones, lymphadenopathy, hepatosplenomegaly, meningeal signs (headache, N/V, visual symptoms; especially in ALL relapse)

Investigations
- CBC: increased leukocytes >10 x 10^9/L (occurs in 50% of patients); neutropenia, anemia, or thrombocytopenia
- may have increased uric acid, K^+, PO_4^{3-}, Ca^{2+}, LDH
- PT, aPTT, fibrinogen, D-dimers for DIC
- leukemic lymphoblasts lack specific morphological (no granules) or cytochemical features, therefore diagnosis depends on immunophenotyping
- cytogenetics: Philadelphia (Ph) chromosome in ~25% of adult ALL cases
- CXR: patients with ALL may have a mediastinal mass
- LP prior to systemic chemotherapy to assess for CNS involvement (ensure adequate platelet count and PT/PTT)

Treatment
- eliminate abnormal cloned cells
  1. Induction: to induce complete remission (undetectable leukemic blasts, restore normal hematopoiesis)
  2. Consolidation and/or intensification of chemotherapy
     - consolidation: continuing same chemotherapy to eliminate subclinical leukemic cells
     - intensification: high doses of different (non-cross-reactive) chemotherapy drugs to eliminate cells with resistance to primary treatment
  3. Maintenance chemotherapy: low dose intermittent chemotherapy over prolonged period (2-3 yr) to prevent relapse
  4. Prophylaxis: CNS radiation therapy or methotrexate (intrathecal or systemic)
     - hematopoietic stem cell transplantation: potentially curative (due to pre-implant myeloablative chemoradiation and post-implant graft-versus-leukemia effect) but relapse rates and non-relapse mortality high

Prognosis
- depends on response to initial induction or if remission is achieved following relapse
- good prognostic factors: young, WBC <30 x 10^9/L, T-cell phenotype, absence of Ph chromosome, early attainment of complete remission
- achievement of first remission: 60-90%
- childhood ALL: 80% long-term remission (>5 yr)
  - higher cure rates in children because of better chemotherapy tolerance, lower prevalence of bcr-abl fusion gene (associated with chemotherapeutic resistance)
- adult ALL: 30-40% 5-yr survival

Table 32. Differentiating AML From ALL

<table>
<thead>
<tr>
<th>AML</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Big people (adults)</td>
<td>Small people (kids)</td>
</tr>
<tr>
<td>Big blasts</td>
<td>Small blasts</td>
</tr>
<tr>
<td>Big mortality rate</td>
<td>Small mortality rate (kids)</td>
</tr>
<tr>
<td>Lots of cytoplasm</td>
<td>Less cytoplasm</td>
</tr>
<tr>
<td>Lots of nucleoli (3-5)</td>
<td>Few nucleoli (1-3)</td>
</tr>
<tr>
<td>Lots of granules and Auer rods</td>
<td>No granules</td>
</tr>
<tr>
<td>Myeloperoxidase, Sudan black stain</td>
<td>PAS (periodic acid-Schiff)</td>
</tr>
<tr>
<td>Maturation defect beyond myeloblast or promyelocyte</td>
<td>Maturation defect beyond lymphoblast</td>
</tr>
</tbody>
</table>

Lymphomas

Definition
- collection of lymphoid malignancies in which malignant lymphocytes accumulate at lymph nodes and lymphoid tissues
  - leading to lymphadenopathy, extranodal disease, and constitutional symptoms

American Society of Hematology
Choosing Wisely Recommendation
Limit surveillance CT scans in asymptomatic patients after curative-intent treatment for aggressive lymphoma
### Table 33. Ann Arbor System for Staging Lymphomas

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of a single lymph node region or extralymphatic organ or site</td>
</tr>
<tr>
<td>II</td>
<td>Involvement of two or more lymph node regions or an extralymphatic site and one or more lymph node regions on same side of diaphragm</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lymph node regions on both sides of the diaphragm; may or may not be accompanied by single extralymphatic site or splenic involvement</td>
</tr>
<tr>
<td>IV</td>
<td>Diffuse involvement of one or more extralymphatic organs including bone marrow</td>
</tr>
</tbody>
</table>

- subtypes
  - A = absence of B-symptoms (see Approach to Lymphadenopathy, H12)
  - B = presence of B-symptoms

### Table 34. Chromosome Translocations

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Gene Activation</th>
<th>Associated Neoplasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(8;14)</td>
<td>c-myc activation</td>
<td>Burkitt’s lymphoma</td>
</tr>
<tr>
<td>t(14;18)</td>
<td>bcl-2 activation</td>
<td>Follicular lymphoma</td>
</tr>
<tr>
<td>t(9;22)</td>
<td>Philadelphia chromosome (bcr-abl hybrid)</td>
<td>CML, ALL in adults (25% of the time)</td>
</tr>
<tr>
<td>t(11;14)</td>
<td>Overexpression of cyclin D1 protein</td>
<td>Mantle cell lymphoma</td>
</tr>
<tr>
<td>t(15;17)</td>
<td>Activation of retinoic acid receptor alpha</td>
<td>Acute promyelocytic leukemia</td>
</tr>
</tbody>
</table>

### Hodgkin Lymphoma

**Definition**
- malignant proliferation of lymphoid cells with Reed-Sternberg cells (thought to arise from germinal centre B-cells)

**Epidemiology**
- bimodal distribution with peaks at 20 yr and >50 yr
- association with Epstein-Barr virus in up to 50% of cases, causal role not determined

**Clinical Features**
- asymptomatic lymphadenopathy (70%)
  - non-tender, rubbery consistency
  - cervical/supraclavicular (60-80%), axillary (10-20%), inguinal (6-12%)
- splenomegaly (50%) ± hepatomegaly
- mediastinal mass
  - found on routine CXR, may be symptomatic (cough)
  - rarely may present with SVC syndrome, pleural effusion
- systemic symptoms
  - B symptoms (especially in widespread disease; fever in 30%), pruritus
  - non-specific/paraneoplastic
    - alcohol-induced pain in nodes, nephrotic syndrome
    - starts at a single site in lymphatic system (node), spreads first to adjacent nodes
  - disease progresses in contiguity with lymphatic system

**Investigations**
- CBC
  - anemia (chronic disease, rarely hemolytic), eosinophilia, leukocytosis, platelets normal or increased early, decreased in advanced disease
  - biochemistry
    - HIV serology
    - LFTs (liver involvement)
    - renal function tests (prior to initiating chemotherapy)
    - ALP, Ca²⁺ (bone involvement)
    - ESR, LDH (monitor disease progression)
- imaging
  - CXR, CT chest (lymph nodes, mediastinal mass), CT abdomen/pelvis (liver or spleen involvement), gallium scan (assess treatment response), PET scans
  - cardiac function assessment (MUGA scan or echocardiography): for patients at high risk of pre-treatment cardiac disease (age >60, history of HTN, CHF, PUD, CAD, MI, CVA), treatment can be cardiotoxic
  - PFTs: if history of lung disease (COPD, smoking, previous radiation to lung)
- excisional lymph node biopsy confirms diagnosis
- bone marrow biopsy to assess marrow infiltration (only necessary if B-symptoms, stage III or IV, bulky disease or cytopenia)
Treatment

- stage I-II: chemotherapy (ABVD) followed by involved field radiotherapy (XRT)
- stage III-IV: chemotherapy (ABVD) with XRT for bulky disease
- relapse, resistant to therapy: high dose chemotherapy, bone marrow transplant
  - new imaging modalities increasingly used including PET scans (follow treatment response)

Complications of Treatment

- cardiac disease: secondary to XRT, adriamycin is also cardiotoxic
- pulmonary disease: secondary to bleomycin (interstitial pneumonitis)
- infertility: recommend sperm banking
- secondary malignancy in irradiated field
  - <2% risk of MDS, AML (secondary to treatment, usually within 8 yr)
  - solid tumours of lung, breast; >8 yr after treatment
- non-Hodgkin lymphoma
- hypothyroidism: post XRT

Prognosis

- Hasenclever adverse prognostic factors:
  1. serum albumin <40 g/L
  2. hemoglobin <105 g/L
  3. male
  4. stage IV disease
  5. age ≥45 yr
  6. leukocytosis (WBC >1.5 x 10⁹/L)
  7. lymphocytopenia (lymphocytes <0.06 x 10⁹/L or <8% of WBC count or both)
- prognostic score
  - each additional adverse prognostic factor decreases freedom from progression at 5 yr (FFP)

Non-Hodgkin Lymphoma

Definition

- malignant proliferation of lymphoid cells of progenitor or mature B- or T-cells

Classification

- multiple classification systems exist at present and may be used at different centres
- can originate from both B- (85%) and T- or NK- (15%) cells
  - B-cell NHL: e.g. diffuse large B-cell lymphoma, follicular lymphoma, Burkitt's lymphoma, mantle cell lymphoma
  - T-cell NHL: e.g. mycosis fungoides, anaplastic large cell lymphoma
- WHO/REAL classification system: 3 categories of NHLs based on natural history
  - indolent (35–40% of NHL): e.g. follicular lymphoma, small lymphocytic lymphoma/CLL, mantle cell lymphoma
  - aggressive (~50% of NHL): e.g. diffuse large B-cell lymphoma
  - highly aggressive (~5% of NHL): e.g. Burkitt's lymphoma

Clinical Features

- painless superficial lymphadenopathy, usually >1 lymph node region
- usually presents as widespread disease (exception is aggressive lymphoma)
- constitutional symptoms not as common as in Hodgkin lymphoma
- cytopenia: anemia ± neutropenia ± thrombocytopenia can occur when bone marrow is involved
- abdominal signs
  - hepatosplenomegaly
  - retroperitoneal and mesenteric involvement (second most common site of involvement)
- oropharyngeal involvement in 5-10% with sore throat and obstructive apnea
- extranodal involvement: most commonly GI tract; also testes, bone, kidney
- CNS involvement in 1% (often with HIV)

Investigations

- CBC
  - normocytic normochromic anemia
  - autoimmune hemolytic anemia
  - advanced disease: thrombocytopenia, neutropenia, and leukoerythroblastic anemia
- peripheral blood film may show lymphoma cells
- flow cytometry of peripheral blood is valuable for low-grade NHL
- biochemistry
  - increase in uric acid
  - abnormal LFTs in liver metastases
  - increased LDH (rapidly progressing disease, poor prognostic factor)
- CXR, CT neck, abdomen, pelvis for staging

International Prognostic Factors Project 1998

<table>
<thead>
<tr>
<th>Prognostic Factors</th>
<th>FFP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>84%</td>
</tr>
<tr>
<td>1</td>
<td>77%</td>
</tr>
<tr>
<td>2</td>
<td>67%</td>
</tr>
<tr>
<td>3</td>
<td>60%</td>
</tr>
<tr>
<td>4</td>
<td>51%</td>
</tr>
<tr>
<td>5-7</td>
<td>42%</td>
</tr>
</tbody>
</table>

FFP = freedom from progression at 5 yr

Treatment of HL depends on stage; treatment of NHL depends on histologic subtype.
• PET is useful for monitoring response to treatment and evaluation of residual tumour following therapy in aggressive histological disease
• diagnosed by
  ▪ lymph node biopsy: excisional biopsy preferred, FNA unreliable
  ▪ bone marrow biopsy: not optimal for diagnosis as BM may not be involved

Treatment
• localized disease (e.g. GI, brain, bone, head and neck)
  ▪ radiotherapy to primary site and adjacent nodal areas
  ▪ adjuvant chemotherapy
  ▪ surgery: splenic marginal zone lymphoma
• indolent lymphoma: goal of treatment is symptom management
  ▪ watchful waiting
  ▪ radiation therapy for localized disease
  ▪ bendamustine plus rituximab, an anti-CD20 antibody, is superior to CHOP + rituximab (CHOP-R) for advanced stage disease (STIL trial)
• aggressive lymphoma: goal of treatment is curative
  ▪ combination chemotherapy: CHOP is mainstay, plus rituximab if B-cell lymphoma
  ▪ radiation for localized/bulky disease
  ▪ CNS prophylaxis with high-dose methotrexate if certain sites involved (testicular, nasopharyngeal)
  ▪ relapse, resistant to therapy: high dose chemotherapy, BMT
• highly aggressive lymphoma
  ▪ Burkitt lymphoma: short bursts of intensive chemotherapy “CODOX-M” chemotherapy regimen also often used ± IVAC with Rituximab
  ▪ CNS prophylaxis and tumour lysis syndrome prophylaxis

Complications
• hypersplenism
• infection
• autoimmune hemolytic anemia and thrombocytopenia
• vascular obstruction (from enlarged nodes)
• bowel perforation
• tumour lysis syndrome (particularly in very aggressive lymphoma) see Tumour Lysis Syndrome H52

Prognosis
• follicular lymphoma: Follicular Lymphoma International Prognostic Index is used (5 adverse prognostic factors): age >60; >4 nodal areas; elevated LDH; Ann Arbor stage III-IV; hemoglobin <120 g/L
  ▪ based on calculated risk, mean 5 yr survival ranges from 53-91%
  ▪ rarely curative, typically relapsing and remitting course with risk of transformation to aggressive lymphomas such as diffuse large B-cell lymphoma
• diffuse large B-cell lymphoma: The International Prognostic Factor Index is used (5 adverse prognostic factors): age >60; Ann Arbor stage (III-IV); performance status (ECOG/Zubrand 2-4); elevated LDH; >1 extranodal site
  ▪ based on calculated risk, mean 5 yr survival ranges from 26-73%
  ▪ ~40% rate of cure

Table 35. Characteristics of Select Non-Hodgkin Lymphomas

<table>
<thead>
<tr>
<th></th>
<th>Follicular Lymphoma</th>
<th>Diffuse Large B-Cell Lymphoma (DLBCL)</th>
<th>Burkitt Lymphoma</th>
<th>Mantle Cell Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of NHLs</td>
<td>22-30%</td>
<td>33%</td>
<td>&lt;1% adult NHLs</td>
<td>6%</td>
</tr>
<tr>
<td>Genetic Mutation</td>
<td>Bcl-2 activation</td>
<td>Bcl-2, Bcl-6, MYC rearrangements</td>
<td>c-myc activation</td>
<td>Overexpression of cyclin D1 (Bcl-1 activation)</td>
</tr>
<tr>
<td>Classification</td>
<td>Indolent</td>
<td>Aggressive (high-grade)</td>
<td>Very aggressive</td>
<td>Indolent</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Middle-age – elderly</td>
<td>Previous CLL (Richter’s transformation: 5% CLL patients progress to DLBCL)</td>
<td>1. Endemic: African origin, EBV-associated</td>
<td>Male (M:F = 4:1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Sporadic: no EBV</td>
<td>3. HIV-related: AIDS-defining illness</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Widespread painless LAD* ± bone marrow involvement</td>
<td>Rapidly progressive LAD and extranodal infiltration</td>
<td>Endemic form: massive jaw LAD</td>
<td>Often presents Stage IV with palpable LAD</td>
</tr>
<tr>
<td></td>
<td>Frequent transformation to aggressive lymphoma</td>
<td>Very responsive to chemoradiation treatment</td>
<td>“Starry-sky” histology</td>
<td>Involvement of GI tract (lymphomatosis polyposis), Waldeyer’s Ring</td>
</tr>
<tr>
<td></td>
<td>High risk of tumour lysis syndrome upon treatment</td>
<td>50% present at stage I/II, 50% widely disseminated</td>
<td>High risk of tumour lysis syndrome upon treatment</td>
<td>5 yr survival 25%</td>
</tr>
</tbody>
</table>

*LAD = lymphadenopathy
### Chronic Lymphocytic Leukemia

**Definition**
- indolent disease characterized by clonal malignancy of mature B-cells

**Epidemiology**
- most common leukemia in Western world
- mainly older patients; median age 65 yr
- M>F

**Pathophysiology**
- accumulation of neoplastic lymphocytes in blood, bone marrow, lymph nodes, and spleen

**Clinical Features**
- 25% asymptomatic (incidental finding)
- 5-10% present with B-symptoms (≥1 of: unintentional weight loss ≥10% of body weight within previous 6 mo, temperature >38°C or night sweats for ≥2 wk without evidence of infection, extreme fatigue)
- lymphadenopathy (50-90%), splenomegaly (25-55%), hepatomegaly (15-25%)
- immune dysregulation: autoimmune hemolytic anemia (Coombs positive), ITP, hypogammaglobulinemia ± neutropenia
- bone marrow failure: late, secondary to marrow involvement by CLL cells

**Investigations**
- CBC: clonal population of CLL lymphocytes >5 x 10⁹/L
- peripheral blood film
  - lymphocytes are small and mature
  - smudge cells
- flow cytometry (CD5, CD20, CD23, etc.)
- cytogenetics: FISH (dictates response therapy and prognosis)
- bone marrow aspirate
  - lymphocytes >30% of all nucleated cells
  - infiltration of marrow by lymphocytes in 4 patterns: nodular (10%), interstitial (30%), diffuse (35%, worse prognosis), or mixed (25%)

**Natural History and Treatment**
- natural history: indolent and incurable; most cases show slow progression
- small minority present with aggressive disease; usually associated with chromosomal abnormalities (e.g. p53 deletion)
- first line therapy is dictated by cytogenetic status and patient co-morbidities
  - observation if early, stable, asymptomatic treatment options vary by region; ideal first line therapy should include a monoclonal CD20 agent (e.g. rituximab, ofatumumab, obinutuzumab)
  - commonly fludarabine + cyclophosphamide + rituximab (FCR) in fit patients with normal CrCl; bendamustine + rituximab (BR) in less fit
  - chlorambucil + anti-CD20 in the elderly
  - corticosteroids, IVIg: especially for autoimmune phenomenonradiotherapy
• molecular therapies
  ▪ Idelalisib – PI3K inhibitor
  ▪ Ibrutinib – BTK (Bruton's tyrosine kinase) inhibitor

Prognosis
• 9 yr median survival, but varies greatly
• prognosis predicted by Rai staging and cytogenetic status
  ▪ low risk: lymphocytosis in blood and bone marrow only
  ▪ intermediate risk: lymphocytosis with enlarged nodes in any site or splenomegaly, hepatomegaly
  ▪ high risk: lymphocytosis with disease-related anemia (<110 g/L) or thrombocytopenia (<100 x 10^9/L)

Complications
• bone marrow failure
• immune complications: AIHA, ITP, immune deficiency (hypogammaglobulinemia, impaired T-cell function)
• polyclonal or monoclonal gammapathy (often IgM)
• hyperuricemia with treatment
• 5% undergo Richter's transformation: aggressive transformation to diffuse large B-cell lymphoma (see Table 35)

Multiple Myeloma

Definition
• neoplastic clonal proliferation of plasma cells producing a monoclonal immunoglobulin resulting in end organ dysfunction
• usually single clone of plasma cells, although biclonal myeloma also occurs; rarely non-secretory

Epidemiology
• incidence 3 per 100,000, most common plasma cell malignancy
• increased frequency with age; median age of diagnosis is 68 yr; M>F

Pathophysiology
• malignant plasma cells secrete monoclonal antibody
  ▪ 95% produce M protein (monoclonal Ig = identical heavy chain + identical light chain, or light chains only)
    ▪ IgG 50%, IgA 20%, IgD 2%, IgM 0.5%
    ▪ 15-20% produce free light chains or light chains alone found in either:
      – serum as an increase in the quantity of either kappa or lambda light chain (with an abnormal kappa:lambda ratio)
      – urine has Bence-Jones protein
  ▪ <5% are non-secretors

Clinical Features and Complications
• bone disease: pain (usually back), bony tenderness, pathologic fractures
  ▪ lytic lesions are classical (skull, spine, proximal long bones, ribs)
  ▪ increased bone resorption secondary to osteoclast activating factors such as PTHrP
• anemia: weakness, fatigue, pallor
  ▪ secondary to bone marrow suppression
• weight loss
• infections
  ▪ usually S. pneumoniae and Gram-negatives
  ▪ secondary to suppression of normal plasma cell function
• hypercalcemia: N/V, confusion, constipation, polyuria, polydipsia
  ▪ secondary to increased bone turnover
• renal disease/renal failure
  ▪ most frequently causes cast nephropathy (see Nephrology, NP31)
• bleeding
  ▪ secondary to thrombocytopenia, may see petechiae, purpura
  ▪ can also be caused by acquired von Willebrand disease
• extramedullary plasmacytoma
  ▪ soft tissue mass composed of monoclonal plasma cells, purplish colour
• hyperviscosity: may manifest as headaches, stroke, angina, MI
  ▪ secondary to increased viscosity caused by M protein

CRAB
Increased Calcium
Renal failure
Anemia
Bony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)

Amyloid
The general term for a variety of proteinaceous materials that have a similar structural organization and are abnormally deposited in tissues
Found in a variety of clinical disorders and can cause systemic (e.g. MM [light chains]) or localized amyloidosis (e.g. Alzheimer disease [AB amyloid])

Hemoglobin
CRAB
Increased Calcium
Renal failure
Anemia
Bony lesions (lytic lesions or osteoporosis felt to be caused by myeloma)
- amyloidosis
  - accumulation of insoluble fibrillar protein (Ig light chain) in tissues; can cause infiltration of any organ system: cardiac infiltration – diastolic dysfunction, cardiac arrhythmias, syncope, sudden death; GI involvement – malabsorption, beefy large or laterally scalloped tongue; neurologic involvement – orthostatic hypotension, carpal tunnel syndrome
  - may cause Factor X deficiency if fibrils bind Factor X → bleeding (raccoon eyes)
- neurologic disease: muscle weakness, pain, paresthesias
  - radiculopathy caused by vertebral fracture, extramedullary plasmacytoma
  - spinal cord compression (10-20% of patients) is a medical emergency

Investigations
- CBC
  - normocytic anemia, thrombocytopenia, leukopenia
  - rouleaux formation on peripheral film
- biochemistry
  - increased Ca\(^{2+}\), increased ESR, decreased anion gap, increased Cr, albumin, \(\beta_2\)-microglobulin (as part of staging), proteinuria (24 h urine collection)
- monoclonal proteins
  - serum protein electrophoresis (SPEP): demonstrates monoclonal protein spike in serum in 80% (i.e. M protein)
  - urine protein electrophoresis (UPEP): demonstrates light chains in urine = Bence-Jones protein (15% secrete only light chains)
  - immunofixation: demonstrates M protein and identifies Ig type; also identifies light chains
  - serum free light chain quantification: kappa and lambda light chains, calculated ratio
- bone marrow aspirate and biopsy
  - often focal abnormality, greater than 10% plasma cells, abnormal morphology, clonal plasma cells; send for FISH or cytogenetics (prognostic implications)
  - skeletal series (x-rays), MRI if symptoms of cord compression
  - presence of lytic lesions and areas at risk of pathologic fracture
  - bone scans are not useful since they detect osteoblast activity
  - \(\beta_2\)-microglobulin, LDH, and CRP are poor prognosticators

Diagnosis
- International Myeloma Working Group Criteria
  1. serum or urinary monoclonal protein
  2. presence of clonal plasma cells in bone marrow or a plasmacytoma
  3. presence of end-organ damage related to plasma cell dyscrasia, such as:
     - increased serum Ca\(^{2+}\)
     - lytic bone lesions
     - anemia
     - renal failure

Treatment
- treatment is non-curative
- treatment goals
  - improvement in quality of life (improve anemia, reverse renal failure, bony pain)
  - prevention of progression and complications
  - increase overall survival
- autologous stem cell transplant if <65 yr old
  - usually preceded by 4-6 mo of cytoreductive therapy: steroid based with novel agents
  - (i.e. immunomodulatory drugs or proteasome inhibitors)
- chemotherapy if >65 yr old or transplant-ineligible
  - melphalan, prednisone, and novel agent (i.e. bortezomib)
- dexamethasone and bortezomib if ARF; bortezomib ± dexamethasone in light chain amyloidosis
- supportive management
  - bisphosphonates for those with osteopenia or lytic bone lesions (requires renal dosing)
  - local XRT for bone pain, spinal cord compression
  - kyphoplasty for vertebral fractures to improve pain relief and regain height
  - treat complications: hydration for hypercalcemia and renal failure, bisphosphonates for severe hypercalcemia, prophylactic antibiotics, erythropoietin for anemia, DVT prophylaxis
- all patients will relapse; choice of retreatment regimen depends on duration of remission, organ involvement, patient's comorbidities, and preferences

Prognosis
- International Staging System (\(\beta_2\)-microglobulin and albumin) used to stage and estimate prognosis
  - cytogenetic profile (i.e. p53 mutation associated with poor survival and resistance to chemotherapy)
  - median survival based on stage, usually 3-7 yr

Routine urinalysis will not detect light chains as dipstick detects albumin. Need sulfosalicylic acid or 24 h urine protein for immunofixation or electrophoresis

Light Chain Disease
15% of MM produce only light chains. Renal failure is a major problem. Kappa > lambda light chain has better prognosis
Monoclonal Gammopathy of Unknown Significance

**Definition**
- presence of M protein in serum in absence of any clinical or laboratory evidence of a plasma cell dyscrasia or lymphoproliferative disorders
  - incidence: 0.15% in general population, 5% of people >70 yr of age
  - asymptomatic

**Diagnosis**
- presence of a serum monoclonal protein (M protein) at a concentration <30 g/L
- <10% plasma cells in bone marrow
- absence of hyperCalcemia, Renal insufficiency, Anemia, Bone disease related to the plasma cell proliferative process (absence of "CRAB")
- 0.3-1% of patients develop a hematologic malignancy each yr
  - patients with M protein peak ≥15 g/L, or patients with IgA or IgM MGUS are at higher risk of malignant transformation
  - patients with abnormal serum free light chains ratio are at increased risk of malignant transformation
- monitor with annual history, physical, CBC, Cr, calcium, albumin, serum protein electrophoresis (considered pre-malignant)

Lymphoplasmacytic Lymphoma (Waldenstrom’s Macroglobulinemia)

**Definition**
- proliferation of lymphoplasmacytoid cells
  - presence of monoclonal IgM paraprotein

**Clinical Features**
- chronic disorder of elderly patients; median age 64 yr
- symptoms: weakness, fatigue, bleeding (oronasal), weight loss, recurrent infections, dyspnea, CHF (triad of anemia, hyperviscosity, plasma volume expansion), neurological symptoms, peripheral neuropathy, cerebral dysfunction
- signs: pallor, splenomegaly, hepatomegaly, lymphadenopathy, retinal lesions
- key complication to avoid: hyperviscosity syndrome
  - because IgM (unlike IgG) confined largely to intravascular space

**Investigations and Diagnosis**
- bone marrow shows plasmacytoid lymphocytes
- bone lesions usually not present
- blood work rarely see hypercalcemia
- cold hemagglutinin disease possible: Raynaud’s phenomenon, hemolytic anemia precipitated by cold weather
- normocytic anemia, rouleaux, high ESR if hyperviscosity not present

**Treatment**
- Bendamustine – R/R-CVP chemotherapy, alkylating agents (chlorambucil), nucleoside analogues (fludarabine), rituximab, or combination therapy
- corticosteroids
- plasmapheresis for hyperviscosity: acute reduction in serum IgM

Complications of Hematologic Malignancies

Hyperviscosity Syndrome

**Definition**
- refers to clinical sequelae of increased blood viscosity (when relative serum viscosity >5-6 units), resulting from increased circulating serum igs or from increased cellular blood components in hyperproliferative disorders (e.g. multiple myeloma, leukemia, PV)
- Waldenstrom’s macroglobulinemia accounts for 85% of cases
Clinical Features
• hypervolemia causing: CHF, headache, lethargy, dilutional anemia
• CNS symptoms due to decreased cerebral blood flow: headache, vertigo, ataxia, stroke
• retina shows venous engorgement and hemorrhages
• bleeding diathesis
  • due to impaired platelet function, absorption of soluble coagulation factors (e.g. nasal bleeding, oozing gums)
• ESR usually very low

Treatment
• plasmapheresis, chemotherapy

Tumour Lysis Syndrome

Definition
• group of metabolic complications that result from spontaneous or treatment-related breakdown of cancer cells
• more common in diseases with large tumour burden and high proliferative rate (high grade lymphoma, leukemia)

Clinical Features
• metabolic abnormalities
  • cells lyse, releasing K\(^+\), uric acid, PO\(_4\)\(^3-\) (increased levels)
  • PO\(_4\)\(^3-\) binds Ca\(^2+\) (decreased Ca\(^2+\))
• complications
  • lethal cardiac arrhythmia (increased K\(^+\))
  • acute renal failure (urate nephropathy, see Nephrology, NP31)

Treatment
• prevention
  • aggressive IV hydration
  • alkalization not recommended due to risk of calcium phosphate or xanthine precipitation in renal tubules
  • allopurinol or rasburicase
  • correction of pre-existing metabolic abnormalities
• dialysis

Blood Products and Transfusions

Blood Products
• RBCs, platelets and coagulation factors (frozen plasma [FP], cryoprecipitate, factor concentrates) are available for transfusion
• donated blood (1 U = 450-500 mL) is fractionated into these various components
  • centrifugation separates whole blood into RBCs and platelet-rich plasma
  • platelet-rich plasma is further fractionated into platelets and plasma
  • need to pool together multiple units to obtain therapeutic amounts
  • FP (previously known as FFP) is plasma frozen within 24 h of collection
  • cryoprecipitate is the high MW precipitate generated when FP is thawed at low temperatures

Specialized Products
• irradiated blood products
  • prevent proliferation of donor T-cells in potential or actual bone marrow transplant recipients
  • used for immunocompromised patients or for patients on purine analogue chemotherapy, first-degree relatives, HLA-matched products and intrauterine transfusions, Hodgkin lymphoma
• CMV-negative blood products
  • potential transplant recipients
  • neonates
  • AIDS patients
  • seronegative pregnant women
**Red Blood Cells**

**Packed Red Blood Cells**
- stored at 4°C
- transfuse within 42 d of collection, otherwise cell lysis may result in hyperkalemia
- infuse each unit over 2 h (max of 4 h)

**Indications for Packed RBC Transfusion**
- Hb <70 g/L; this may change as per patient’s tolerance or symptoms
- maintain Hb between 70 and 100 g/L during active bleeds
- consider maintaining a higher Hb for patients with:
  - CAD/unstable coronary syndromes
  - uncontrolled, unpredictable bleeding
  - impaired pulmonary function
  - increased O₂ consumption

**Selection of Red Cells for Transfusion**
- when anticipating an RBC transfusion, the following should be ordered:
  - group and screen: determines the blood group and Rh status of the recipient as well as the presence of autoantibodies vs. major/minor blood group antigens in the patient’s serum
  - cross-match: involves mixing the recipient’s blood with potential donor blood and looking for agglutination (takes 30–45 min)
- when blood is required, several options are available
  - 1ˢᵗ line: fully crossmatched blood, electronic crossmatch is becoming more widely used (not always available in emergency situations)
  - 2ⁿᵈ line: donor blood of the same group and Rh status as the recipient
  - 3ʳᵈ line: O- blood for females of reproductive age; O+ blood for all others

**Platelets**

**Table 37. Platelet Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random donor (pooled)</td>
<td>Thrombocytopenia with bleeding</td>
</tr>
<tr>
<td>Single donor platelets</td>
<td>Potential BMT recipients</td>
</tr>
<tr>
<td>HLA matched platelets</td>
<td>Refractory to pooled or single donor platelets, presence of HLA antibodies</td>
</tr>
</tbody>
</table>

- stored at 20–24°C
- random donor platelets are transfused from a pool of 4 units; this should increase the platelet count by ≥15 x 10⁹/L
- single donor platelets (transfused as single units) should increase the platelet count by 40–60 x 10⁹/L
- if an increase in the platelet count is not seen post-transfusion: autoantibodies (i.e. ITP), alloantibodies, consumption (bleeding, sepsis), or hypersplenism may be present

**Table 38. Indications for Platelet Transfusion**

<table>
<thead>
<tr>
<th>Plt (x 10⁹/L)</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>Non-immune thrombocytopenia</td>
</tr>
<tr>
<td>&lt;20</td>
<td>Procedures not associated with significant blood loss</td>
</tr>
<tr>
<td>&lt;50</td>
<td>Procedures associated with blood loss or major surgery (&gt;500 mL EBL)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>Pre-neurosurgery or head trauma</td>
</tr>
<tr>
<td>Any</td>
<td>Platelet dysfunction (or antiplatelet agents) and marked bleeding</td>
</tr>
</tbody>
</table>

**Relative Contraindications of Platelet Transfusion**
- TTP, HIT, post-transfusion purpura, HELLP

---

**American Society of Hematology**

Choosing Wisely Recommendation

Do not transfuse more than the minimum number of RBC units necessary to relieve symptoms of anemia or to return the patient to a safe hemoglobin range (70-90 g/L) in stable non-cardiac patients

**Transfusion Requirements in Critical Care (TRICC)**

NEJM 1999;340:409-417

Study: Multicentre, RCT.

Participants: 838 critically ill patients with euvolemia after initial treatment and hemoglobin less than 9 g/dL, within 72 h of ICU admission.

Intervention: Patients receiving a transfusion followed either (1) a restrictive strategy (RS; n=418) in which red cells were transfused if hemoglobin was less than 7.0 g/dL, and then maintained at 7 to 9 g/dL or (2) a liberal strategy (LS; n=420) in which transfusions occurred when the hemoglobin was less than 10.0 g/dL. and then maintained at 10 to 12 g/dL.

Primary Outcome: Mortality at 30 d and severity of organ dysfunction.

Results: Mortality rates at 30 d were similar between groups. However, mortality rates were significantly lower with the RS among less acutely ill patients (8.7% RS and 16.1% in LS group; p=0.03) and among those <59 yr of age (5.7% RS and 13% in LS; p=0.02), but did not differ in a subgroup with clinically significant cardiac disease.

Conclusion: A RS of red cell transfusion is at least as effective as, and possibly superior to, a LS transfusion in critically ill patients.

---

**Liberal or Restrictive Transfusion in High-Risk Patients After Hip Surgery (FOCUS)**

NEJM 2011;365:2453-2462

Study: Multicentre RCT.

Participants: 2,016 patients aged greater than 50 yr with a history of or risk factors for cardiovascular disease and hemoglobin (Hb) level below 10 g/dL after hip fracture surgery.

Intervention: Patients were randomly assigned to a liberal transfusion strategy (a Hb threshold of 10 g/dL) or a restrictive transfusion strategy (anemia symptoms or at physician discretion for a Hb level less than 8 g/dL). Primary Outcome: Mortality or inability to walk across a room without human assistance on a 60 day follow-up.

Results: Primary outcome rates were 35.2% in the liberal transfusion strategy group and 34.7% in the restrictive transfusion strategy group. Rates of complications were similar in the two groups.

Conclusion: A liberal transfusion strategy did not reduce mortality rates or the inability to walk independently on 60 d follow-up compared to a restrictive transfusion strategy in elderly patients with high cardiovascular risk factors after hip surgery.
Coagulation Factors

Table 39. Coagulation Factor Products

<table>
<thead>
<tr>
<th>Product</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frozen plasma (FP)</td>
<td>Depletion of multiple coagulation factors (e.g., sepsis, DIC, dilution, TTP/HUS, liver disease), emergency reversal of life-threatening bleeding secondary to warfarin overdose</td>
</tr>
<tr>
<td>Cryoprecipitate (enriched fibrinogen, vWF, VIII, XIII)</td>
<td>Factor VIII deficiency, von Willebrand disease, Hypofibrinogenemia</td>
</tr>
<tr>
<td>Hemate P</td>
<td>von Willebrand disease</td>
</tr>
<tr>
<td>Factor VIII concentrate</td>
<td>Factor VIII deficiency (Hemophilia A)</td>
</tr>
<tr>
<td>Factor IX concentrate</td>
<td>Factor IX deficiency (Hemophilia B)</td>
</tr>
<tr>
<td>Recombinant FIlla</td>
<td>Factor VII deficiency with bleeding, Hemophilia A or B with inhibitors</td>
</tr>
<tr>
<td>Prothrombin complex (Octaplex®)</td>
<td>Reversal of warfarin therapy or vitamin K deficiency in bleeding patient or patient requiring urgent (&lt;6 h) surgical procedure</td>
</tr>
</tbody>
</table>

Acute Blood Transfusion Reactions

IMMUNE

Acute Hemolytic Transfusion Reactions

- ABO incompatibility resulting in intravascular hemolysis secondary to complement activation, occurs immediately after transfusion
- most commonly due to incorrect patient identification
- risk per unit of blood is <1 in 40,000
- presentation: fever, chills, hypotension, back or flank pain, dyspnea, hemoglobinuria
- acute renal failure (<24 h) and DIC
- treatment
  - stop transfusion
  - notify blood bank and check for clerical error
  - maintain BP with vigorous IV fluids ± inotropes
  - maintain urine output with diuretics, crystalloids, dopamine

Febrile Nonhemolytic Transfusion Reactions

- due to alloantibodies to WBC, platelets or other donor plasma antigens, and release of cytokines from blood product cells
- occurs within 0-6 h of transfusion
- risk per unit of blood is 1 in 100 (minor), 1 in 10,000 to 40,000 (severe)
- presents with fever ± rigors, facial flushing, headache, myalgia, hypotension
- treatment
  - rule out hemolytic reaction or infection
  - if temperature <38°C, continue with transfusion but decrease rate and give antipyretics
  - if temperature >38°C, stop transfusion, give antipyretics and anti-histamine

Allergic Nonhemolytic Transfusion Reactions

- alloantibodies (IgE) to proteins in donor plasma result in mast cell activation and release of histamine
- occurs mainly in those with history of multiple transfusions or multiparous women
- risk per unit of blood is 1 in 100
- presents mainly as urticaria and occasionally with fever
- can present as anaphylactoid reaction with bronchospasm, laryngeal edema, and hypotension, but this occurs mainly in IgA deficient patients that have anti-IgA antibodies
- treatment
  - mild: slow transfusion rate and give diphenhydramine
  - moderate to severe: stop transfusion, give IV diphenhydramine, steroids, epinephrine, IV fluids, and bronchodilators

Transfusion-Related Acute Lung Injury

- new-onset acute lung injury that occurs during transfusion or within 6 h of transfusion completion
  - insidious, acute onset of pulmonary insufficiency
  - profound hypoxemia (PaO₂/FiO₂ <300 mmHg)
  - bilateral pulmonary edema on CXR
  - pulmonary artery wedge pressure <18 mmHg
  - no clinical evidence of left atrial hypertension
  - pathogenesis uncertain; perhaps due to binding of donor antibodies to WBC of recipient and release of mediators that increase capillary permeability in the lungs
  - typically occurs 2-4 h post transfusion and resolves in 24-72 h
  - risk per unit of blood is 1 in 10,000
  - is currently the leading cause of transfusion-related morbidity and mortality
  - treatment: supportive therapy (oxygen)
  - inform blood bank; patient and donor testing will be arranged
NONIMMUNE

Transfusion-Associated Circulatory Overload
- due to impaired cardiac function and/or excessive rapid transfusion
- presentation: dyspnea, orthopnea, hypotension, tachycardia, crackles at base of lung, and increased venous pressure
- incidence: 1 in 700 and is becoming more common
- treatment: transfuse at lower rate, give diuretics and oxygen

Bacterial Infection
- Gram positive: *S. aureus, S. epidermidis, Bacillus cereus*
- Gram negative: *Klebsiella, Serratia, Pseudomonas, Yersinia*
- overall risk is 1 in 100,000 for RBC and 1 in 10,000 for platelets
- never store blood >4 h after bag has left blood bank
- treatment: stop transfusion, blood cultures, IV antibiotics, fluids

Hyperkalemia
- due to K+ release from stored RBC
- risk increases with storage time and if blood is irradiated and risk decreases if given fresh blood
- occurs in 5% of massively transfused patients
- treatment: see Nephrology, NP12

Citrate Toxicity
- occurs with massive transfusion in patients with liver disease – patients are unable to clear citrate from blood
- citrate binds to Ca^{2+} and causes signs and symptoms of hypocalcemia
- treatment: IV calcium gluconate (10 mL for every 2 units of blood)

Dilutional Coagulopathy
- occurs with massive transfusion (>10 units)
- pRBC contains no clotting factors, fibrinogen, cryoprecipitate, or platelets
- treatment: FP, cryoprecipitate, and platelets

Delayed Blood Transfusion Reactions

IMMUNE

Delayed Hemolytic
- due to alloantibodies to minor antigens such as Rh, Kell, Duffy, and Kidd
- level of antibody at time of transfusion is too low to cause hemolysis; later the level of antibody increases due to secondary stimulus and causes extravascular hemolysis
- occurs 5-7 d after transfusion
- presentation: anemia and mild jaundice
- treatment: no specific treatment required; important to note for future transfusion

Transfusion-Associated Graft Versus Host Disease
- transfused T-lymphocytes recognize and react against “host” (recipient)
- occurs 4-30 d following transfusion
- most patients already have severely impaired immune systems (e.g. Hodgkin lymphoma or leukemia)
- presentation: fever, diarrhea, liver function abnormalities, and pancytopenia
- can be prevented by giving irradiated blood products

NONIMMUNE

Iron Overload
- due to repeated transfusions over long period of time (e.g. β-thalassemia major)
- can cause secondary hemochromatosis
- treatment: iron chelators or phlebotomy if no longer requiring blood transfusion and not anemic

Viral Infection Risk
- HBV <1 in 153,000
- Human T-lymphotropic virus (HTLV) <1 in 4,300,000
- HCV <1 in 2,300,000
- HIV <1 in 7,000,000
- other infections include EBV, CMV, WNV (West Nile virus)
### Antiplatelet Therapy

- see Figure 11a, *Platelet Activation Cascade*, H26

#### Figure 15. Mechanisms of action of antiplatelet therapy

<table>
<thead>
<tr>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspirin® (ASA)</strong></td>
<td>Irreversibly acetylates COX, inhibiting TXA2 synthesis, thus inhibiting platelet aggregation</td>
<td>Single loading 200-300 mg PO, followed by dose of 75-100 mg PO daily</td>
<td>Onset: 5-30 min Peak: 0.25-3 h Duration: 3-6 h</td>
<td>GI ulcer/bleeding Tinnitus Bronchospasm Angioedema Reye’s syndrome in pediatric patients</td>
</tr>
<tr>
<td><strong>Aggrenox® (ASA + Dipyridamole)</strong></td>
<td>Dipyridamole increases intracellular cAMP levels, which inhibits TXA2 synthesis, leading to decreased platelet aggregation</td>
<td>1 capsule PO bid</td>
<td>Peak: 75 min</td>
<td>H/A Dyspepsia N/V Abdominal pain Cardiac failure Hemorrhoids</td>
</tr>
<tr>
<td><strong>Clopidogrel (Plavix®)</strong></td>
<td>Inhibit ADP binding to platelets, thus decreased platelet aggregation</td>
<td>75-300 mg PO daily</td>
<td>Onset: 2 h Peak: 1 h</td>
<td>URI Chest pain H/A Flu-like syndrome Depression UTI GI hemorrhage Pancytopenia May cause TTP</td>
</tr>
<tr>
<td><strong>Glycoprotein IIb/IIIa Inhibitors (ReoPro® [abciximab], Integrelin® [epti])</strong></td>
<td>Blocking GP IIb/IIIa receptor inhibits fibrinogen and vWF binding, leading to decreased platelet aggregation</td>
<td>Variable IV</td>
<td>Variable</td>
<td>Hypotension Back pain N/V Chest pain Abdominal pain Thrombocytopenia</td>
</tr>
</tbody>
</table>
## Anticoagulant Therapy

### Table 41. Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism of Action</th>
<th>Dose/Route of Administration</th>
<th>Onset/Peak/Duration</th>
<th>Reversing Agent</th>
<th>Monitoring</th>
<th>Specific Side Effects</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Heparin</strong></td>
<td>Accelerates activity of antithrombin</td>
<td>As per hospital nomogram</td>
<td>Onset: 20-60 min Peak: 2-4 h</td>
<td>Protamine sulfate</td>
<td>aPTT (intrinsic pathway), UFH (anti-Xa) levels</td>
<td>Hemorrhage, HIT</td>
<td>Increased liver enzymes</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Vitamin K antagonist: inhibits production of II, VII, IX, X, proteins C and S</td>
<td>Individualized dosing by monitoring PT/INR PO</td>
<td>Onset: 36-48 h Peak: 1.5-3 d</td>
<td>IV vitamin K</td>
<td>PT/INR maintain 2-3 (2.5-3.5 for mechanical values)</td>
<td>Hemorrhage</td>
<td>Cholesterol embolism syndrome Intraocular hemorrhage</td>
</tr>
<tr>
<td><strong>LMWH</strong> (enoxaparin, dalteparin, tinzaparin)</td>
<td>Inhibits FXa</td>
<td>Variable SC/IV</td>
<td>Onset: 3-5 h Peak: 3-5 h Duration: 12 h</td>
<td>Partial reversibility with protamine sulfate</td>
<td>FXa in pediatrics, pregnancy and weight &gt;150 kg</td>
<td>Hemorrhage, Fever</td>
<td>Increased liver enzymes &lt;1% HIT</td>
</tr>
<tr>
<td><strong>Fondaparinux</strong></td>
<td>Selective inhibitor of FXa</td>
<td>Variable SC daily</td>
<td>Onset: 2 h Peak: 2-3 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Anemia, Fever, Nausea, Rash</td>
<td>Heparin analogue Contraindicated in renal failure</td>
</tr>
<tr>
<td><strong>Rivaroxaban</strong></td>
<td>Anti-FXa</td>
<td>PO</td>
<td>Peak: 2.4 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Syncope, GI hemorrhage</td>
<td>Indicated in treatment of acute VTE (non-cancer patients), secondary VTE prevention, thromboembolysis in orthopedic patients and stroke prophylaxis in non-valvular AFT; ensure CrCl&gt;30</td>
</tr>
<tr>
<td><strong>Apixaban</strong></td>
<td>Anti-FXa</td>
<td>PO</td>
<td>Onset: 3-4h Peak: 3-4 h</td>
<td>Not reversible</td>
<td>None</td>
<td>Hemorrhage, Nausea, Anemia</td>
<td>Indicated for stroke prophylaxis in non-valvular AFT; Idiopathic VTE; ensure CrCl &gt;30</td>
</tr>
<tr>
<td><strong>Argatroban</strong></td>
<td>Direct thrombin inhibitor</td>
<td>Variable IV</td>
<td>Onset: 5-10 min Peak: 3-15 min</td>
<td>Not reversible</td>
<td>aPTT</td>
<td>Dyspnea, Hypotension, Fever</td>
<td>Indicated for HIT, renal failure, unstable patients</td>
</tr>
<tr>
<td><strong>Dabigatran</strong></td>
<td>Direct thrombin inhibitor</td>
<td>150 mg PO bid</td>
<td>Peak: 1 h</td>
<td>Not reversible</td>
<td>None (prolonged aPTT can suggest residual drug on board)</td>
<td>GI upset, Dyspepsia</td>
<td>Only indicated for AFT in Canada Contraindicated in renal failure, cancer patients, mechanical heart valves</td>
</tr>
</tbody>
</table>

### Adverse Reactions of Heparin
- Hemorrhage: depends on dose, age, and concomitant use of antiplatelet agents or thrombolytics
- Heparin-induced thrombocytopenia: associated with venous or arterial thrombosis (see Table 22, H29)
- Osteoporosis: with long-term use

### Low Molecular Weight Heparin (enoxaparin, dalteparin, tinzaparin)
- Increased bioavailability compared to normal heparin
- Increased duration of action
- SC route of administration
- Do not need to monitor aPTT
- Adverse reactions less common than UFH
- Patients with renal failure (CrCl <30) can accumulate LMWH, therefore must adjust dose
- Only partially reversible with protamine sulfate

### Table 42. Recommended Therapeutic INR Ranges of Common Indications for Oral Anticoagulant Therapy

<table>
<thead>
<tr>
<th>Indication</th>
<th>INR Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prophylaxis of venous thrombosis (high-risk surgery)</td>
<td>2.0-3.0</td>
</tr>
<tr>
<td>Treatment of venous thrombosis</td>
<td></td>
</tr>
<tr>
<td>Most cases of thrombosis with antiphospholipid antibody syndrome</td>
<td></td>
</tr>
<tr>
<td>Treatment of pulmonary embolism</td>
<td></td>
</tr>
<tr>
<td>Prevention of systemic embolism</td>
<td></td>
</tr>
<tr>
<td>Tissue heart valves</td>
<td></td>
</tr>
<tr>
<td>AMI (to prevent systemic embolism)</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td></td>
</tr>
<tr>
<td>Bileaflet mechanical valve in aortic position</td>
<td></td>
</tr>
<tr>
<td>Mechanical prosthetic mitral valves (high risk)</td>
<td>2.5-3.5</td>
</tr>
<tr>
<td>Prophylaxis of recurrent myocardial infarction</td>
<td></td>
</tr>
</tbody>
</table>

**Table 42 continued...**
### Table 43. Recommended Management of a Supratherapeutic INR

<table>
<thead>
<tr>
<th>INR</th>
<th>Bleeding Present</th>
<th>Recommended Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;Therapeutic to 4.5</td>
<td>No</td>
<td>Lower warfarin dose OR Omit a dose and resume warfarin at a lower dose when INR is in therapeutic range OR No dose reduction needed if INR is minimally prolonged</td>
</tr>
<tr>
<td>&gt;4.5 to 10.0</td>
<td>No</td>
<td>Omit the next 1 to 2 doses of warfarin, monitor INR more frequently and resume treatment at a lower dose when INR is in therapeutic range OR Omit a dose and administer 1 to 2.5 mg oral vit K in patients with increased risk of bleeding</td>
</tr>
<tr>
<td>&gt;10.0</td>
<td>No</td>
<td>Hold warfarin and administer 5 to 10 mg oral vit K; monitor INR more frequently and administer more vit K as needed; resume warfarin at a lower dose when INR is in therapeutic range</td>
</tr>
<tr>
<td>Any</td>
<td>Serious or life threatening</td>
<td>Hold warfarin and administer 10 mg vit K by slow IV infusion; supplement with four-factor prothrombin complex concentrate; monitor and repeat as needed</td>
</tr>
</tbody>
</table>

Adapted from: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;142 suppl:e1S25

### Table 44. Selected Chemotherapeutic and Biologic Agents Used in Oncology

<table>
<thead>
<tr>
<th>Class</th>
<th>Example</th>
<th>Mechanism of Action or Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alkylating Agent</td>
<td>• chlorambucil, cyclophosphamide, melphalan (nitrogen mustards)</td>
<td>Damage DNA via alkylation of base pairs Leads to cross-linking of bases, abnormal base-pairing, DNA breakage</td>
</tr>
<tr>
<td></td>
<td>• carmustine, cisplatin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• dacarbazine, procarbazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• busulfan</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• bendamustine</td>
<td></td>
</tr>
<tr>
<td>Antimetabolites</td>
<td>• methotrexate (folic acid antagonist)</td>
<td>Inhibit DNA synthesis</td>
</tr>
<tr>
<td></td>
<td>• 6-mercaptopurine, fludarabine (purine antagonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• 5-fluorouracil (5-FU) (pyrimidine antagonist)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• hydroxyurea</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• cytarabine</td>
<td></td>
</tr>
<tr>
<td>Antibiotics</td>
<td>• adriamycin (anthracycline)</td>
<td>Interfere with DNA and RNA synthesis</td>
</tr>
<tr>
<td></td>
<td>• bleomycin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• mitomycin C</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• daunorubicin</td>
<td></td>
</tr>
<tr>
<td>Taxanes</td>
<td>• paclitaxel</td>
<td>Stabilize microtubules against breakdown once cell division complete</td>
</tr>
<tr>
<td></td>
<td>• docetaxel</td>
<td></td>
</tr>
<tr>
<td>Vinca-alkaloids</td>
<td>• vinblastine</td>
<td>Inhibit microtubule assembly (mitotic spindles), blocking cell division</td>
</tr>
<tr>
<td></td>
<td>• vincristine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• vinorelbine</td>
<td></td>
</tr>
<tr>
<td>Topoisomerase Inhibitors</td>
<td>• irinotecan, topotecan (topo I)</td>
<td>Interfere with DNA unwinding necessary for normal replication and transcription</td>
</tr>
<tr>
<td></td>
<td>• etoposide (topo II)</td>
<td></td>
</tr>
<tr>
<td>Steroids</td>
<td>• prednisone</td>
<td>Immunosuppression</td>
</tr>
<tr>
<td></td>
<td>• dexamethasone</td>
<td></td>
</tr>
<tr>
<td>Purine Anallogues</td>
<td>• fludarabine</td>
<td>Interferes with DNA synthesis</td>
</tr>
<tr>
<td></td>
<td>• cladribine</td>
<td></td>
</tr>
<tr>
<td>Monoclonal Antibodies</td>
<td>• trastuzumab (Herceptin®)</td>
<td>HER2 antagonist</td>
</tr>
<tr>
<td></td>
<td>• bevacizumab (Avastin®)</td>
<td>VEGF antagonist</td>
</tr>
<tr>
<td></td>
<td>• rituximab (Rituxan®), ofatumumab (Arzerra®), obinutuzumab (Gazyva®)</td>
<td>CD20 antagonist</td>
</tr>
<tr>
<td></td>
<td>• cetuximab (Erbix®)</td>
<td>EGFR antagonist</td>
</tr>
<tr>
<td>Small Molecule Inhibitors</td>
<td>• imatinib mesylate (Gleevec®)</td>
<td>Bcr-Abl inhibitor</td>
</tr>
<tr>
<td></td>
<td>• dasatinib</td>
<td>Bcr-Abl inhibitor</td>
</tr>
<tr>
<td></td>
<td>• nilotinib</td>
<td>Bcr-Abl inhibitor</td>
</tr>
<tr>
<td></td>
<td>• erlotinib (Tarceva®)</td>
<td>EGFR antagonist</td>
</tr>
<tr>
<td></td>
<td>• gefitinib (Iressa®)</td>
<td>EGFR antagonist</td>
</tr>
<tr>
<td></td>
<td>• bortezomib (Velcade®)</td>
<td>26S proteasome inhibitor</td>
</tr>
<tr>
<td></td>
<td>• sunitinib (Sutent®)</td>
<td>VEGF, PDGFR antagonist</td>
</tr>
<tr>
<td></td>
<td>• ibrutinib (Imbruvica®)</td>
<td>BTK inhibitor</td>
</tr>
<tr>
<td></td>
<td>•idealasib (Zydelig®)</td>
<td>P13K inhibitor</td>
</tr>
<tr>
<td></td>
<td>• ruxolitinib (Jakavi®)</td>
<td>JAK2 inhibitor</td>
</tr>
</tbody>
</table>
### Landmark Hematology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematologic Malignancies and Related Disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hodgkin Lymphoma: ABVD vs. MOPP</td>
<td>NEJM 1992; 327:1478-84</td>
<td>In Hodgkin lymphoma, ABVD regimen has equal failure-free and overall survival to MOPP + ABVD, but less myelotoxicity; ABVD is standard chemotherapy for Hodgkin lymphoma.</td>
</tr>
<tr>
<td>CHOP</td>
<td>NEJM 1993; 328:1002-6</td>
<td>In NHL, CHOP has lowest incidence of fatal toxic reactions and shows no significant difference from 3 other regimens in response or disease-free/overall survival; CHOP is the standard for advanced NHL.</td>
</tr>
<tr>
<td>R-CHOP</td>
<td>NEJM 2002; 346:235-42</td>
<td>Addition of rituximab to CHOP increases complete response rate and prolongs event-free survival and overall survival in elderly with DLBCL.</td>
</tr>
<tr>
<td>CML: Imatinib vs. IFN + Cytarabine</td>
<td>NEJM 2003; 348:994-1004</td>
<td>In patients with chronic-phase CML, imatinib was more effective than IFN + cytarabine in inducing cytogenetic response and freedom from progression to accelerated phase/blast crisis.</td>
</tr>
<tr>
<td>CLL8</td>
<td>Lancet 2010; 376:1164-74</td>
<td>Rituximab plus fludarabine and cyclophosphamide (FCR) improves progression-free and overall survival compared with fludarabine and cyclophosphamide alone (FC) in the treatment of CLL.</td>
</tr>
<tr>
<td>VISTA</td>
<td>JCO 2010; 28:2259-66</td>
<td>Bortezomib plus melphalan and prednisone (MPV) is superior to melphalan and prednisone (MP) in overall survival of non-transplant-eligible myeloma patients.</td>
</tr>
<tr>
<td>CYTO-PV</td>
<td>NEJM 2013; 369(1):22-33</td>
<td>In patients with polycythemia vera, a hemarcit target of &lt; 0.45 for cytoreductive therapy is associated with prevention of thrombotic complications.</td>
</tr>
<tr>
<td>StIL</td>
<td>Lancet 2013; 381(9873):1203-10</td>
<td>Bendamustine plus rituximab is superior to R-CHOP in terms of progression-free survival and fewer toxic effects in patients with previously untreated indolent lymphoma.</td>
</tr>
<tr>
<td>Ibrutinib vs. Ofatumumab in previously treated CLL</td>
<td>NEJM 2014; 371:213-223</td>
<td>Ibrutinib, as compared with ofatumumab, significantly improved progression-free survival, overall survival, and response rate among patients with previously treated CLL or SLL.</td>
</tr>
<tr>
<td><strong>Trombosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLOT</td>
<td>NEJM 2003; 349:146-53</td>
<td>In patients with cancer and acute venous thromboembolism, LWMH was more effective than warfarin in reducing the risk of recurrent thromboembolism without increasing the risk of bleeding.</td>
</tr>
<tr>
<td>PT1</td>
<td>NEJM 2005; 353:85-6</td>
<td>Hydroxyurea plus low-dose ASA is superior to anagrelide plus low-dose ASA for patients with essential thrombocythemia at high risk for vascular events.</td>
</tr>
<tr>
<td>ESPIRIT</td>
<td>Lancet 2006; 367:1865-73</td>
<td>ASA plus dipyridamole is recommended over ASA alone as antithrombotic therapy after cerebral ischemia of arterial origin.</td>
</tr>
<tr>
<td>Dabigatran vs. Warfarin in VTE</td>
<td>NEJM 2009; 361:2342-52</td>
<td>In the treatment of venous thromboembolism, dabigatran is as effective as warfarin and also has a similar safety profile; note: many problems in the trial, making it less pivotal in having drug approval.</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>NEJM 2012; 366:1287-1297</td>
<td>Among patients with acute PE, rivaroxaban is noninferior to warfarin in preventing recurrent VTE, and is associated with similar bleeding rates.</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>NEJM 2013; 369:799-808</td>
<td>In patients with VTE who have completed 6-12 months of anticoagulation, long-term apixaban treatment reduces recurrent VTE or all-cause mortality without increasing rates of major bleeding.</td>
</tr>
<tr>
<td><strong>Blood Products and Transfusion</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet Transfusion Threshold</td>
<td>NEJM 1997; 337:1870-5</td>
<td>The risk of major bleeding in patients with AML undergoing induction chemotherapy was similar whether the platelet-transfusion threshold was set at 20 or 10; use of the lower threshold reduced platelet usage by 21.5%.</td>
</tr>
<tr>
<td>TRICC BP</td>
<td>NEJM 1999; 340:409-17</td>
<td>A restrictive strategy of red-cell transfusion (when Hb &lt; 70) is at least as effective as and possibly superior to a liberal transfusion strategy (when Hb &lt;100) in ICU patients; one possible exception is patients with an acute MI or unstable angina.</td>
</tr>
<tr>
<td>Dose of Platelet Transfusion</td>
<td>NEJM 2010; 362:600-13</td>
<td>Low dose prophylactic platelet transfusion decreases total number of platelets transfused but increases number of transfusions but not incidence of bleeding in patients with hypoproliferative thrombocytopenia.</td>
</tr>
<tr>
<td>Transfusion in High-Risk Patients after Hip Surgery</td>
<td>NEJM 2011; 365:2453-2462</td>
<td>A liberal transfusion strategy (Hb &lt;100), as compared with a restrictive strategy (anemia symptoms or at physician discretion for Hb &lt;80), did not reduce rates of death or inability to walk independently on 60-day follow-up or reduce in-hospital morbidity in elderly patients at high cardiovascular risk.</td>
</tr>
<tr>
<td>Therapeutic Platelet Transfusion</td>
<td>Lancet 2012; 380:1309-16</td>
<td>Therapeutic platelet transfusions (when bleeding occurs) may be used if severe bleeding can be identified early in autologous stem-cell transplant patients; prophylactic transfusion (when platelets &lt;10) should remain standard of care in AML patients.</td>
</tr>
<tr>
<td>Transfusion Strategies for Acute Upper GI Bleeding</td>
<td>NEJM 2013; 368:11-21</td>
<td>As compared with a liberal transfusion strategy (Hb &lt;90), a restrictive strategy (Hb&lt;70) significantly improved outcomes in patients with acute upper gastrointestinal bleeding.</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MSH</td>
<td>NEJM 1995; 332:1317-22</td>
<td>Hydroxyurea is effective in reduction of complications and clinical manifestations of sickle cell disease.</td>
</tr>
<tr>
<td>ITP: Dexamethasone</td>
<td>NEJM 2003; 349:831-6</td>
<td>A four-day course of high-dose dexamethasone is effective initial therapy for adults with immune thrombocytopenic purpura.</td>
</tr>
<tr>
<td>CRASH-2</td>
<td>Health Technol Assess 2013; 17(10):1-79</td>
<td>Early administration of TXA safely reduced the risk of death in bleeding trauma patients and is highly cost-effective. Treatment beyond 3 hours of injury is unlikely to be effective.</td>
</tr>
</tbody>
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Bacteria Basics

- bacteria are prokaryotic cells that divide asexually by binary fission
- Gram stain divides most bacteria into two groups based on their cell wall
  - Gram positive (GP): thick, rigid layer of peptidoglycan
  - Gram negative (GN): thin peptidoglycan layer + thicker outer membrane composed of lipopolysaccharides
- clinical significance: GN thick outer membrane makes it resistant to penicillin's mechanism of action
- acid-fast bacilli (AFB): high mycolic acid content in cell wall, "acid fast" as washout phase with acid-alcohol is ineffective in acid-fast bacteria, e.g. Mycobacteria, Nocardia
- *atypical* bacteria: not seen on Gram stain and difficult to culture
- obligate intracellular bacteria: e.g. Chlamydia, Chlamyphilia
- bacteria lacking a cell wall: e.g. Mycoplasma
- spirochetes: e.g. Treponema pallidum
- O₂ can be either vital or detrimental to growth
- obligate aerobes: require O₂
- obligate anaerobes: require environment without O₂
- facultative anaerobes: can survive in environments with or without O₂

Mechanisms of Bacterial Disease

1. adherence to and colonization of skin or mucous membranes
   - e.g. fimbiae (pili): microfilaments extending through the cell wall – like burrs sticking to your clothes, they attach to epithelial cells e.g. E. coli in the urinary tract
2. invasion or crossing normal epithelial barriers
3. evasion of host defense system through inhibition of
   - phagocytic uptake via polysaccharide capsule (S. pneumoniae, N. meningitidis, H. influenzae) or surface proteins (Staphylococcus, Streptococcus)
4. toxin production
   - exotoxins are secreted by living pathogenic bacteria and cause disease even if the bacteria is not present (e.g. Clostridium)
   - endotoxins are structural components of GN bacterial cell walls, and may be shed by live cells or released during cell lysis
5. intracellular growth
   - obligate intracellular: Rickettsia, Chlamydia, Chlamyphilia
   - facultative intracellular: Salmonella, Neisseria, Brucella, Mycobacteria, Listeria, Legionella
6. biofilm
   - an extracellular polysaccharide network forming mesh around the bacteria (e.g. S. epidermidis) which can coat prosthetic devices like IV catheters
Table 1. Common Bacteria

<table>
<thead>
<tr>
<th>Gram-Positive Bacteria</th>
<th>Gram-Negative Bacteria</th>
<th>Not Seen on Gram Stain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerobes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coeci</td>
<td>Bacilli (rods)</td>
<td>Diplococci</td>
</tr>
<tr>
<td>Staphylococcus</td>
<td>Bacillus</td>
<td>Neisseria</td>
</tr>
<tr>
<td>S. aureus</td>
<td>B. anthracis</td>
<td>N. meningitidis</td>
</tr>
<tr>
<td>S. saprophyticus</td>
<td>Listeria</td>
<td>N. gonorrhoeae</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>Nocardia (modified acid fast positive)</td>
<td>Bacillus</td>
</tr>
<tr>
<td>Streptococcus</td>
<td></td>
<td>Moraxella</td>
</tr>
<tr>
<td>S. pneumoniae (GAS)</td>
<td></td>
<td>M. catarrhalis</td>
</tr>
<tr>
<td>S. agalactiae (GBS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterococcus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E. fecalis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>Peptostreptococcus</td>
<td>Clostridium</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C. difficile, C. tetani, C. botulinum, C. perfringens</td>
</tr>
</tbody>
</table>

Table 2. Commensal Flora

<table>
<thead>
<tr>
<th>Site</th>
<th>Organisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Coagulase-negative staphylococci, Corynebacterium, Propionibacterium acnes, Bacillus, S. aureus</td>
</tr>
<tr>
<td>Oropharynx</td>
<td>Viridans group streptococci, Haemophilus, Neisseria, anaerobes (Peptostreptococcus, Bacteroides, Veillonella, Fusobacterium, Actinomyces, Prevotella)</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>E. coli, anaerobes (low numbers)</td>
</tr>
<tr>
<td>Colon</td>
<td>E. coli, Klebsiella, Enterobacter, Enterococcus, anaerobes (Bacteroides, Peptostreptococcus, Clostridium)</td>
</tr>
<tr>
<td>Vagina</td>
<td>Lactobacillus acidophilus, viridans group streptococci, coagulase-negative staphylococci, facultative Gram-negative bacilli, anaerobes</td>
</tr>
</tbody>
</table>

Figure 2. Laboratory identification of bacterial species
Virology

Viral Basics
- Viruses are infectious particles consisting of RNA or DNA covered by a protein coat
  - Infect cells and use host metabolic machinery to replicate
  - Nucleic acid can be double stranded (ds) or single stranded (ss)
  - Can be enveloped or naked
- Virions are mature virus particles that can be released into the extracellular environment
- Host susceptibility is governed by the host cell and virus surface proteins (viral tropism) and cellular immunity

Viral Disease Patterns
1. Acute infections (e.g. adenovirus)
   - Host cells are lysed in the process of virion release
   - Some produce acute infections with late sequelae (e.g. measles virus → subacute sclerosing panencephalitis)
2. Chronic infections (>6 mo): (e.g. HBV, HIV)
   - Host cell machinery is used to produce and chronically release virions
3. Latent infections
   - Viral genome remains latent in host cell nucleus
   - Can reactivate (e.g. HSV, VZV)

Table 3. Common Viruses

<table>
<thead>
<tr>
<th>Nucleic Acid</th>
<th>Enveloped</th>
<th>Virus Family</th>
<th>Major Virus</th>
<th>Medical Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsDNA</td>
<td>N</td>
<td>Adenoviridae</td>
<td>Adenovirus</td>
<td>URTI, Conjunctivitis, Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Papillomaviridae</td>
<td>HPV1, 4</td>
<td>Plantar warts</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Papillomaviridae</td>
<td>HPV6, 11</td>
<td>Genital warts</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Papillomaviridae</td>
<td>HPV16, 18, etc.</td>
<td>Cervical/anal dysplasia and cancer</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV1 = HSV1</td>
<td>Oral, ocular, and genital herpes; encephalitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV2 = HSV2</td>
<td>Oral, genital, and oral herpes; encephalitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV3 = VZV</td>
<td>Chicken pox, shingles</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV4 = EBV</td>
<td>Mononucleosis, viral hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV5 = CMV</td>
<td>Retinitis, pneumonia, hepatitis, encephalitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV6*</td>
<td>Rosola</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Herpesviridae</td>
<td>HHV8 = KSHV</td>
<td>Kaposi’s sarcoma, multicentric Castlemann’s disease, body cavity lymphoma</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Polyomaviridae</td>
<td>JC virus</td>
<td>Progressive multifocal leukoencephalopathy</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Hepadnaviridae</td>
<td>Hepatitis B</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Papovaviridae</td>
<td>Papovavirus B19</td>
<td>Erythema infectiosum (Fifth disease)</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Paroviridae</td>
<td>Parvovirus B19</td>
<td>Erythema infectiosum (Fifth disease)</td>
</tr>
<tr>
<td>(+) ssRNA</td>
<td>N</td>
<td>Caliciviridae</td>
<td>Norwalk</td>
<td>Gastroenteritis</td>
</tr>
<tr>
<td></td>
<td>N</td>
<td>Caliciviridae</td>
<td>Hepatitis E</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Picornaviridae</td>
<td>Poliovirus</td>
<td>Poliomyelitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Picornaviridae</td>
<td>Echovirus</td>
<td>URTs, viral meningitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Picornaviridae</td>
<td>Rhinovirus</td>
<td>URTs</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Picornaviridae</td>
<td>Coxsackie virus</td>
<td>Hand-foot-and-mouth, viral meningitis, myocarditis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Picornaviridae</td>
<td>Hepatitis A</td>
<td>Acute hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Coronaviridae</td>
<td>Coronavirus</td>
<td>URTs, SARS, MERS</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>Yellow fever</td>
<td>Yellow fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>Dengue fever</td>
<td>Dengue fever</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>Hepatitis C</td>
<td>Hepatitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Flaviviridae</td>
<td>West Nile</td>
<td>Encephalitis, flaccid paralysis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Togaviridae</td>
<td>Rubella</td>
<td>Rubella (German measles)</td>
</tr>
<tr>
<td>(+) ssRNA-RT</td>
<td>Y</td>
<td>Retroviridae</td>
<td>HIV</td>
<td>AIDS</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Retroviridae</td>
<td>HTLV-I</td>
<td>T-cell leukemia and lymphoma</td>
</tr>
<tr>
<td>(+) ssRNA</td>
<td>Y</td>
<td>Arenaviridae</td>
<td>Lassa fever</td>
<td>Lassa fever</td>
</tr>
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<td></td>
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<td>Ebola, Marburg</td>
<td>Hemorrhagic fever</td>
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<td></td>
<td>Y</td>
<td>Orthomyxoviridae</td>
<td>Influenza A, B, C</td>
<td>Influenza</td>
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<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Measles</td>
<td>Measles</td>
</tr>
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<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>Mumps</td>
<td>Mumps</td>
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<td>Paramyxoviridae</td>
<td>Parainfluenza</td>
<td>URTs, croup, bronchiolitis</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Paramyxoviridae</td>
<td>RSV</td>
<td>Bronchiolitis, pneumonia</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>Rhabdoviridae</td>
<td>Rabies</td>
<td>Rabies</td>
</tr>
<tr>
<td>dssRNA</td>
<td>N</td>
<td>Reoviridae</td>
<td>Rotavirus</td>
<td>Gastroenteritis</td>
</tr>
</tbody>
</table>

Note: _virdae = family, _virus = genus, # = species (e.g. Retroviridae HIV-2)
Mycology

Fungal Basics
- fungi are eukaryotic organisms, they can have the following morphologies
  1. yeast (unicellular)
  2. molds (also known as filamentous fungi) (multicellular with hyphae)
  3. dimorphic fungi (found as mold at room temperature but grow as yeast-like forms at body temperature)

Table 4. Membrane and Cell Wall Compositions

<table>
<thead>
<tr>
<th>Membrane Sterol</th>
<th>Cell Wall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteria</td>
<td>Peptidoglycan</td>
</tr>
<tr>
<td>Human Cell</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Fungi</td>
<td>Ergosterol, Chitin</td>
</tr>
</tbody>
</table>

Mechanisms of Fungal Disease
- primary fungal infection by
  - overgrowth of normal flora (e.g. Candida species)
  - inhalation of fungal spores
  - traumatic inoculation into skin
- toxins produced by fungi (e.g. ingestion aflatoxins)
- allergic reactions to fungi (e.g. bronchopulmonary aspergillosis)

Parasitology

Parasite Basics
- parasite: an organism that lives in or on another organism (host) and damages the host in the process
- parasites with complex life cycles require more than one host to reproduce
  - reservoir host: maintains a parasite and may be the source for human infection
  - intermediate host: maintains the asexual stage of a parasite or allows development of the parasite to proceed through the larval stages
  - definitive host: allows the parasite to develop to the adult stage where reproduction occurs
- 2 major groups of parasites: protozoa and helminths
- see Tables 26 and 27 for examples of clinically important parasites

Table 5. Differences Between Protozoa and Helminths

<table>
<thead>
<tr>
<th>Protozoa</th>
<th>Helminths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unicellular</td>
<td>Multicellular</td>
</tr>
<tr>
<td>Motile trophozoite → inactive cyst</td>
<td>Adult → egg → larva</td>
</tr>
<tr>
<td>Multiplication</td>
<td>No multiplication</td>
</tr>
<tr>
<td>Eosinophilia unusual</td>
<td>Eosinophilia (proportional to extent of tissue invasion)*</td>
</tr>
<tr>
<td>Indefinite life span</td>
<td>Definite life span</td>
</tr>
</tbody>
</table>

*Adult Ascaris (roundworm) does not cause eosinophilia; migratory larval phases of Ascaris, however, cause high-grade eosinophilia

Characteristics of Parasitic Disease
- symptoms are usually proportional to parasite burden
- tissue damage is due to the parasite and host immune response
- chronic infections may occur with or without overt disease
- immunocompromised hosts are more susceptible to manifestations of infection, reactivation of latent infections, and more severe disease
- eosinophilia may suggest a parasitic infection

Mechanisms of Parasitic Disease
1. mechanical obstruction (e.g. ascariasis, clonorchiasis)
2. competition with host for resources (e.g. anemia in hookworm disease, vitamin B12 deficiency in diphyllobothriasis)
3. cytotoxicity leading to abscesses and ulcers (e.g. amoebiasis, leishmaniasis)
4. inflammatory
  - acute hypersensitivity (e.g. pneumonitis in Loeffler’s syndrome)
  - delayed hypersensitivity (e.g. egg granulomas in schistosomiasis)
  - cytokine-mediated (systemic illness of malaria, disseminated strongyloidiasis)
5. immune-mediated injury
  - autoimmune (e.g. myocarditis of Chagas disease, tissue destruction of mucocutaneous leishmaniasis)
  - immune complex (e.g. nephritis of malaria, schistosomiasis)
### Transmission of Infectious Diseases

**Table 6. Mechanism of Transmission**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Mode of Transmission</th>
<th>Examples</th>
<th>Preventative Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contact</td>
<td>Direct physical contact, or indirect contact with a fomite</td>
<td>Skin-to-skin (MRSA)</td>
<td>For patients in health care facilities: Contact precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sexual (N. gonorrhoeae, C. trachomatis, HSV, HIV)</td>
<td>Barrier precautions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blood-borne (HIV, HBV, HCV)</td>
<td>Safe needlestick/sharp practices</td>
</tr>
<tr>
<td>Droplet/Contact</td>
<td>Respiratory droplets (&gt;5 µm) can be projected short distances (≤2 m) and deposit on mucosal surfaces of the recipient (e.g. by coughing, sneezing, or talking); transmission can also occur by direct physical contact of respiratory fluids or indirect contact with a fomite contaminated with respiratory fluids</td>
<td>Influenza, mumps N. meningitidis, Bordetella pertussis</td>
<td>For patients in health care facilities: Contact/droplet precautions</td>
</tr>
<tr>
<td>Airborne</td>
<td>Airborne droplet nuclei (&lt;5 µm) remain infectious over time and distance</td>
<td>M. tuberculosis, VZV, measles</td>
<td>For patients in health care facilities: Airborne precautions</td>
</tr>
<tr>
<td>Food/Waterborne</td>
<td>Ingestion of contaminated food or water</td>
<td>V. cholerae, Salmonella, HAV, HEV</td>
<td>Prophylactic vaccinations where available</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ensure clean food/water supply</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For patients in health care facilities: Contact precautions used for admitted patients with fecal incontinence when stool is unable to be contained in diapers</td>
</tr>
<tr>
<td>Zoonotic</td>
<td>Disease transmission from animals to humans either directly or via an insect vector</td>
<td>Animals (rabies, Q fever) Arthropods (malaria, Lyme disease)</td>
<td>Prophylactic medications, vaccinations</td>
</tr>
<tr>
<td>Vertical</td>
<td>Spread of disease from parent to offspring</td>
<td>Congenital syndromes (TORCH infections) Perinatal (HIV, HBV, GBS)</td>
<td>Prenatal screening</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prophylactic treatment</td>
</tr>
</tbody>
</table>

### Nosocomial Infections

- **nosocomial infection**: infections acquired >48 h after admission to a healthcare facility or within 30 d from discharge
- risk factors: prolonged hospital stay, antibiotic use, surgery, hemodialysis, intensive care, colonization with a resistant organism, immunodeficiency
- patients with nosocomial infections have higher mortality, longer hospital stays, and higher healthcare costs
- hand hygiene is an essential precaution

**Table 7. Common Nosocomial Infectious Agents**

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Characteristics</th>
<th>Manifestation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methicillin-Resistant S. aureus (MRSA)</td>
<td>Gram-positive cocci</td>
<td>Skin and soft tissue infection Bacteremia Pneumonia Endocarditis Osteomyelitis</td>
<td>Admission screening culture from nares and peri-anal region identifies colonization Culture of infection site CXR</td>
<td>Contact precautions For infection: vancomycin or daptomycin or linezolid To decolonize: 2% chlorhexidine wash OD (+ rifampin + (doxycycline or TMP/SMX) + mupirocin cream bid to nares) x 7 d</td>
</tr>
<tr>
<td>Vancomycin-Resistant Enterococcus (VRE)</td>
<td>Majority are E. faecium Resistant if minimum inhibitory concentration of vancomycin is ≥32 µg/mL</td>
<td>Rarely causes disease in healthy people UTI Bacteremia Endocarditis Meningitis</td>
<td>Rectal or perirectal swab OR stool culture for colonization Culture of infected site</td>
<td>Contact precautions* Ampicillin if susceptible Otherwise, linezolid, tigecycline, or daptomycin depending on site of infection No effective decolonization methods identified</td>
</tr>
</tbody>
</table>
Table 7. Common Nosocomial Infectious Agents (continued)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>Characteristics</th>
<th>Manifestation</th>
<th>Investigations</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clostridium difficile</em> (C. difficile)</td>
<td>Releases exotoxins A and B and a hypervirulent strain has been responsible for increase in incidence and severity</td>
<td>Fever, nausea, abdominal pain and watery diarrhea plus occult blood</td>
<td>Stool PCR for toxin B gene and stool immunoassay for toxins A and B (less sensitive than PCR)</td>
<td>Contact precautions and hand hygiene</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Watery diarrhea and pseudomembranous colitis</td>
<td>AXR (may see colonic dilatation) and sigmoidoscopy for pseudomembranes; avoid if known colonic dilatation</td>
<td>Supportive therapy (IV fluids) and general surgical consult</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severe: toxic megacolon and risk of bowel perforation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Associated with antibiotic use and leukocytosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended Spectrum β-lactam Producers (ESBL producing <em>E. coli, K. pneumoniae</em>)</td>
<td>Resistant to most β-lactam antibiotics except carbapenems and e.g. penicillins, actinomycins, and cephalosporins</td>
<td>UTI and pulmonary infection and bacteremia</td>
<td>Blood, sputum, urine, or aspirated body fluid culture</td>
<td>Carbenem or non-β-lactam antibiotics can be used for empiric therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liver abscess in susceptible patients and meningitis</td>
<td>Imaging at infection site (CXR, CT, U/S)</td>
<td></td>
</tr>
</tbody>
</table>

Respiratory Infections

Pneumonia

- see *Pediatrics*, P88
- see *Family Medicine*, FM20

**Definition**

- infection of the lung parenchyma

**Etiology and Risk Factors**

- impaired lung defenses
  - poor cough/gag reflex (e.g. illness, drug-induced)
  - impaired mucociliary transport (e.g. smoking, cystic fibrosis)
  - immunosuppression (e.g. steroids, chemotherapy, AIDS/HIV, DM, transplant, cancer)
- increased risk of aspiration
- impaired swallowing mechanism (e.g. impaired consciousness, neurologic illness causing dysphagia, mechanical obstruction)

- no organism identified in 75% of hospitalized cases, and >90% of ambulatory cases

**Table 8. Common Organisms in Pneumonia**

<table>
<thead>
<tr>
<th>Community-Acquired</th>
<th>Nosocomial</th>
<th>Aspiration</th>
<th>Immunosuppressed Patients</th>
<th>Alcoholic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical Bacteria</td>
<td>Streptococcus pneumoniae</td>
<td>Enteric GNB (e.g. <em>E. coli</em>)</td>
<td>Oral anaerobes (e.g. <em>Bacteroides</em>)</td>
<td>Pneumocystis jiroveci Fungi (e.g. CMV, HSV)</td>
</tr>
<tr>
<td></td>
<td>Moraxella catarrhalis</td>
<td>Pseudomonas aeruginosa</td>
<td>Enteric GNB (e.g. <em>E. coli</em>)</td>
<td>Nocardia</td>
</tr>
<tr>
<td></td>
<td>Haemophilus influenzae</td>
<td><em>S. aureus</em> (including MRSA)</td>
<td><em>S. aureus</em></td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>GAS</td>
<td>Gastric contents (chemical pneumonia)</td>
<td>TB</td>
</tr>
<tr>
<td>Atypical Bacteria</td>
<td><em>Mycoplasma pneumoniae</em></td>
<td>Legionella pneumophila</td>
<td>Viral Influenza virus</td>
<td>Klebsiella</td>
</tr>
<tr>
<td></td>
<td><em>Chlamydia pneumoniae</em></td>
<td><em>Legionella pneumophila</em></td>
<td>Adenovirus</td>
<td>Enteric GNB</td>
</tr>
<tr>
<td></td>
<td>Viral</td>
<td><em>Influenza virus</em></td>
<td></td>
<td><em>S. aureus</em></td>
</tr>
<tr>
<td></td>
<td>Adenovirus</td>
<td></td>
<td></td>
<td>Oral anaerobes (aspiration)</td>
</tr>
</tbody>
</table>

*See *Pediatrics* P90, Table for Common Causes and Treatment of Pneumonia at Different Ages

**Clinical Features**

- cough (± sputum), fever, pleuritic chest pain, dyspnea, tachypnea, tachycardia
- elderly often present atypically; altered LOC is sometimes the only sign
- evidence of consolidation (dullness to percussion, bronchial breath sounds, crackles)
- features of parapneumonic effusion (decreased air entry, dullness to percussion) (see Respiratory R23)
- complications: ARDS, lung abscess, parapneumonic effusion/empyema, pleuritis ± hemorrhage
Investigations
- pulse oximetry to assess severity of respiratory distress
- CBC and differential, electrolytes, urea, Cr, ABG (if respiratory distress), troponin/CK, LFTs, urinalysis
- sputum Gram stain/C&S, blood C&S, ± serology/viral detection, ± pleural fluid C&S (if effusion >5 cm or respiratory distress)
- CXR±CT chest shows distribution (lobar consolidation or interstitial pattern), extent of infiltrate ± cavitation
- bronchoscopy ± washings for
  1. (1) severely ill patients refractory to treatment and (2) immunocompromised patients

Treatment
- ABC, O₂, IV fluids, consider salbutamol (nebulized or MDI)
- determine prognosis and need for hospitalization and antibiotics

Criteria for Hospitalization

Table 9. CURB 65 Score – Pneumonia Clinical Prediction Tool

<table>
<thead>
<tr>
<th>Component</th>
<th>Measurement(s)</th>
<th>Points</th>
<th>Total Score</th>
<th>Mortality</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>Altered mental status</td>
<td>1</td>
<td>0-1</td>
<td>&lt;5%</td>
<td>Can treat as outpatient</td>
</tr>
<tr>
<td>Urea/BUN</td>
<td>Urea &gt; 7 mmol/L or BUN &gt; 20 mg/dL</td>
<td>1</td>
<td>2-3</td>
<td>5-15%</td>
<td>Consider hospitalization</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>&gt; 30 breaths/min</td>
<td>1</td>
<td>4-5</td>
<td>15-30%</td>
<td>Consider ICU</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Systolic &lt; 90 or diastolic &lt; 60 mmHg</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>65 or older</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 10. IDSA/ATS Community Acquired Pneumonia Treatment Guidelines 2007

<table>
<thead>
<tr>
<th>Setting</th>
<th>Circumstances</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatient</td>
<td>Previously well, No antibiotic use in last 3 mo</td>
<td>Macrolide¹ OR Doxycycline</td>
</tr>
<tr>
<td>Comorbidities²</td>
<td>Antibiotic use in last 3 mo (use different class)</td>
<td>Respiratory fluoroquinolone³ OR β-lactam² + Macrolide¹</td>
</tr>
<tr>
<td>Inpatient</td>
<td>Ward</td>
<td>Respiratory fluoroquinolone³ OR β-lactam² + Macrolide¹</td>
</tr>
<tr>
<td>ICU</td>
<td></td>
<td>β-lactam² + (Macrolide¹ OR Respiratory fluoroquinolone³)</td>
</tr>
</tbody>
</table>

Table 11. IDSA/ATS Hospital/Ventilator/Healthcare-Associated Pneumonia Treatment Guidelines 2005

<table>
<thead>
<tr>
<th>Setting</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No risk factors for multidrug resistance (MDR) Early onset (&lt;5 d)</td>
<td>Ceftriaxone OR levofloxacin, moxifloxacin, or ciprofloxacin OR ampicillin/subbactam OR ertapenem</td>
</tr>
<tr>
<td>Late onset disease (≥5 d) or With risk factors for MDR:</td>
<td>Antipseudomonal cephalosporin (ceftepipe or ceftazidime) OR antipseudomonal carbapenem (imipenem or meropenem) OR β-lactam/β-lactamase inhibitor (piperacillin/tazobactam) PLUS</td>
</tr>
</tbody>
</table>

Note: Always use directed therapy against specific organism if one is found on culture (e.g. blood, sputum, etc.)
Note: These guidelines may be less applicable in Canada given lower rates of antibiotic resistance among common nosocomial pathogens

Prevention
- Public Health Agency of Canada recommends the following
  1. Vaccine for influenza A and B annually for all ages ≥ 6 mo
  2. Pneumococcal polysaccharide vaccine (Pneumovax®) for all adults ≥ 65 yr and younger patients 24 mo of age and older at high risk for invasive pneumococcal disease (e.g. functional or anatomic asplenia, congenital or acquired immunodeficiency)
pneumococcal conjugate vaccine (Prevnar-13®) for all children <5 yr, and for children and adolescents at high risk for invasive pneumococcal disease who are 5-17 yr and who have not previously received Prevnar-13® (CDC recommends giving Prevnar-13® to all adults at high risk for invasive pneumococcal disease)

### Influenza

**Definitions and Etiology**
- influenza viruses A and B
- influenza A further divided into subtypes based on envelope glycoproteins: hemagglutinin (H) and neuraminidase (N)
- seasonal (epidemic) influenza
  - main circulating influenza viruses: human-origin A (H1N1) and B (H3N2) subtypes
  - associated with antigenic drift (gradual, minor changes due to random point mutations)
  - may create a new viral subtype resulting in a seasonal epidemic (disease prevalence is greater than expected)
- outbreaks occur mainly during winter months (late December to early March)
- pandemic influenza
  - associated with antigenic shift: abrupt, major changes due to mixing of two different viral strains from different hosts
  - may create a new viral strain resulting in a pandemic outbreak (worldwide)
- antigenic shift occurs only in type A
- transmission: droplet, possibly airborne

**Clinical Features**
- incubation period 1-4 d
- acute onset of systemic (fever, chills, myalgias, arthralgias, H/A, fatigue) and respiratory symptoms (cough, dyspnea, pharyngitis)
- complications: respiratory (viral pneumonia, secondary bacterial pneumonia, otitis media, sinusitis), muscular (rhabdomyolysis, myositis), neurologic (encephalitis, meningitis, transverse myelitis, Guillain-Barré syndrome)

**Investigations**
- diagnosis is primarily clinical based on symptoms during the influenza season
- nasopharyngeal swabs for rapid antigen detection, DFA (Direct Fluorescent Antigen) detection, RT-PCR (gold standard)
- serology: rarely used for clinical management

**Treatment and Prevention**
- primarily supportive unless severe infection or high-risk of complications (e.g. elderly, pulmonary or cardiac disease)
- neuraminidase inhibitors: zanamivir (Relenza®) and oseltamivir (Tamiflu)® for treatment and prophylaxis against types A and B
  - decreases duration (by 1-2 d) and severity of symptoms if given within 48 h of onset
  - treatment beyond 48 h time window may be warranted in immunosuppressed and critically ill patients
- M2-inhibitors: amantidine/rimantidine for treatment and prophylaxis against type A only no longer recommended due to increased resistance
- vaccine for influenza A and B viruses is recommended annually for all ages ≥6 mo
- vaccine is reformulated each year to reflect circulating influenza A and B strains

### Cellulitis

**Definition**
- acute infection of the skin principally involving the dermis and subcutaneous tissue
Etiology
- common causative agents: *S. aureus*, β-hemolytic streptococci
- immunocompromised patients or water exposure: may also include GN rods and fungi
- risk factors
  - trauma with direct inoculation, recent surgery
  - peripheral vascular disease, lymphedema DM, cracked skin in feet/toes (tinea pedis)

Clinical Features
- pain, edema, erythema with indistinct borders ± regional lymphadenopathy, systemic symptoms (fevers, chills, malaise)
- can lead to ascending lymphangitis (visible red streaking in skin along lymphatics proximal to area of cellulitis)

Investigations
- CBC and differential, blood C&S if febrile
- skin swab ONLY if open wound with pus

Treatment
- antibiotics: cephalaxin (broader coverage if risk factors for GN rods)
- if extensive erythema or systemic symptoms, consider cefazolin IV
- if MRSA is suspected, alternative therapy should be prescribed (see *A Simplified Look at Antibiotics*, ID47)
- limb rest and elevation may help reduce swelling

Necrotizing Fasciitis

Definition
- life- and limb-threatening infection of the deep fascia characterized by rapid spread

Etiology
- Two main forms
  - Type I: polymicrobial infection – aerobes and anaerobes (e.g. *S. aureus*, *Bacteroides*, *Enterobacteriaceae*)
  - Type II: monomicrobial infection with GAS, and less commonly *S. aureus*

Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
- edema, ± crepitus (subcutaneous gas from anaerobes), ± fever
- infection spreads rapidly
- patients may rapidly become very sick (tachycardia, hypotension, lightheadedness)
- late findings
  - skin turns dusky blue and black (secondary to thrombosis and necrosis)
  - induration, formation of hemorrhagic bullae

Investigations
- clinical/surgical diagnosis – do NOT wait for results of investigations before beginning treatment
- blood and tissue C&S
- serum CK (elevated CK usually means myonecrosis – a late sign)
- plain film x-ray (soft tissue gas may be visualized)
- surgical exploration for debridement of infected tissue

Treatment
- resuscitation with IV fluids
- emergency surgical debridement to confirm diagnosis and remove necrotic tissue (may require amputation)
- IV antibiotics
  - unknown organism: meropenem or piperacillin/tazobactam + clindamycin IV ± vancomycin
  - if MRSA is considered
  - Type I (polymicrobial): piperacillin/tazobactam + clindamycin IV
  - Type II (monomicrobial): cefazolin (or cloxacillin) + clindamycin IV; with confirmed GAS infection, penicillin G + clindamycin IV
  - with Type II, evaluate for streptococcal toxic shock syndrome and the need for IVIg

Gastrointestinal Infections

Acute Diarrhea
- see *Gastroenterology*, G15
- see *Pediatrics*, P35
Epidemiology
• one of the top five leading causes of death worldwide, according to the World Health Organization
• significant morbidity in developed countries (over 900,000 hospitalizations in the United States each year)

Definition
• passage of ≥3 loose or liquid stools/d OR >200 g stool/d for >2 d but ≤14 d

Approach to Acute Diarrhea
• rationale
  ▪ the vast majority of acute diarrhea is caused by infection
  ▪ in most cases, acute diarrheal illness is viral and/or self-limited, and lasts <3 d
  ▪ investigations are costly and are necessary only in certain circumstances
• therefore, the evaluation of acute diarrhea involves
  ▪ identifying characteristics of the illness or patient that warrant further investigation
  ▪ assessing volume status to determine appropriate method of rehydration
• see Figure 7

Physical Exam
• volume status: appearance, level of alertness, pulse, BP, orthostatic vitals, JVP, mucous membranes, skin turgor, capillary refill
• abdominal exam: pain, guarding, peritoneal signs

Treatment
• rehydration is mainstay of treatment
  ▪ oral rehydration therapy
  ▪ IV rehydration if oral intake insufficient to replace fluid loss
• antidiarrheal agents reduce duration of diarrhea: loperamide, bismuth salicylate
  ▪ delays excretion of causative pathogens
  ▪ contraindications: diarrhea with fever, bloody stool or diarrhea caused by C. difficile
• antibiotic therapy is rarely indicated because
  ▪ most acute diarrheal illness is viral and self-limited
  ▪ antibiotics can eradicate normal gut flora, predisposing patient to C. difficile infection
  ▪ antibiotics prolong the shedding of Salmonella and other causes of bacterial diarrhea
  ▪ in EHEC infection, antibiotics may increase the risk of HUS
  ▪ indications for antibiotic therapy are shown in Figure 7

Figure 7. Approach to acute diarrhea

Causes of Acute Bloody Diarrhea
Campylobacter
Hemorrhagic E. coli (e.g. O157:H7)
Entamoeba histolytica
Salmonella
Shigella
### Table 13. Bacteria in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>B. cereus</em> – Type A (emetic)</td>
<td>1-6 h</td>
<td>–</td>
<td>+</td>
<td>&lt;12 h</td>
<td>None</td>
</tr>
<tr>
<td><em>B. cereus</em> – Type B (diarrheal)</td>
<td>8-16 h</td>
<td>–</td>
<td>–</td>
<td>&lt;24 h</td>
<td>None</td>
</tr>
<tr>
<td>Campylobacter jejuni</td>
<td>2-10 d</td>
<td>+</td>
<td>±</td>
<td>&lt;1 wk</td>
<td></td>
</tr>
<tr>
<td>Clostridium difficile</td>
<td>Unclear</td>
<td>±</td>
<td>±</td>
<td>Variable</td>
<td></td>
</tr>
<tr>
<td>Clostridium perfringens</td>
<td>8-12 h</td>
<td>±</td>
<td>–</td>
<td>&lt;24 h</td>
<td>None</td>
</tr>
<tr>
<td>Enteroinvasive <em>E. coli</em> (EIEC)</td>
<td>1-3 d</td>
<td>±</td>
<td>+</td>
<td>7-10 d</td>
<td>None</td>
</tr>
<tr>
<td>Enterotoxigenic <em>E. coli</em> (ETEC)</td>
<td>1-3 d</td>
<td>–</td>
<td>+</td>
<td>3 d</td>
<td>Fluoroquinolone or azithromycin for moderate to severe symptoms</td>
</tr>
<tr>
<td>Enterohemorrhagic <em>E. coli</em> (EHEC) i.e. O157:H7</td>
<td>3-8 d</td>
<td>–</td>
<td>+</td>
<td>5-10 d</td>
<td>None: antibiotics increase risk of HUS</td>
</tr>
<tr>
<td>Salmonella typhi</td>
<td>10-14 d</td>
<td>+</td>
<td>±</td>
<td>&lt;5-7 d</td>
<td>Empiric treatment with ceftriaxone or azithromycin Fluoroquinolone resistance is increasing</td>
</tr>
<tr>
<td>Salmonella paratyphi (i.e. Enteric Fever, Typhoid)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-typhoidal Salmonellosis <em>S. typhimurium, S. enteritidis</em></td>
<td>12-72 h</td>
<td>+</td>
<td>±</td>
<td>3-7 d</td>
<td>Ciprofloxacin only in severe illness, extremes of age, joint protheses, valvular heart disease, severe atherosclerosis, cancer, uremia</td>
</tr>
<tr>
<td>Shigella dysenteriae</td>
<td>1-4 d</td>
<td>+</td>
<td>±</td>
<td>&lt;1 wk</td>
<td>Fluoroquinolone</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>2-4 h</td>
<td>–</td>
<td>+</td>
<td>1-2 d</td>
<td>None</td>
</tr>
<tr>
<td><em>Vibrio cholerae</em></td>
<td>1-3 d</td>
<td>–</td>
<td>–</td>
<td>3-7 d</td>
<td>Tetracycline or quinolones (ciprofloxacin)</td>
</tr>
<tr>
<td>Yersinia</td>
<td>5 d</td>
<td>+</td>
<td>±</td>
<td>Up to 3 wk</td>
<td>Fluoroquinolone only for severe illness</td>
</tr>
</tbody>
</table>

**Notes**: Preformed exotoxin
Secondary endotoxin
Can develop pseudomembranous colitis
Shiga toxin production Monitor renal function: 10% develop HUS Antidiarrheals increase risk of HUS
Very small inoculum needed for infection Complications include toxic megacolon, HUS Antidiarrheals may increase risk of toxic megacolon
Majority of cases in children 1-4 yr Mesenteric adenitis and terminal ileitis can occur without diarrhea, mimicking appendicitis

*ID12 Infectious Diseases Gastrointestinal Infections Toronto Notes 2016*
Table 14. Parasites in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptosporidium</td>
<td>Fecal-oral</td>
<td>7 d ±</td>
<td>– – +</td>
<td>1-20 d</td>
<td>Paromomycin + nitazoxanide</td>
<td>Immune reconstitution if immunosuppressed</td>
</tr>
<tr>
<td>Entamoeba histolytica</td>
<td>Worldwide endemic areas</td>
<td>2-4 wk ±</td>
<td>– + – ±</td>
<td>Variable</td>
<td>Metronidazole + iodoquinol or paromomycin if symptomatic infection Only iodoquinol or paromomycin for asymptomatic cyst passage</td>
<td>If untreated, potential for liver abscess Sigmoidoscopy shows flat ulcers with yellow exudates</td>
</tr>
<tr>
<td>Giardia lamblia</td>
<td>Fecal-oral Contaminated food/water</td>
<td>1-4 wk – –</td>
<td>+ +</td>
<td>Variable</td>
<td>Metronidazole or nitazoxanide Treatment of asymptomatic carriers not recommended</td>
<td>Higher risk in: day care children, intake of untreated water (“beaver fever”), MSM, immunodeficiency (decreased IgA) May need duodenal biopsy</td>
</tr>
</tbody>
</table>

Toronto Notes 2016

Table 15. Viruses in Infectious Diarrhea

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Source or Mode of Transmission</th>
<th>Incubation</th>
<th>Clinical Features</th>
<th>Duration</th>
<th>Antimicrobial Therapy</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>Fecal-oral</td>
<td>24 h – –</td>
<td>+ +</td>
<td>24 h</td>
<td>None</td>
<td>Noroviruses includes Norwalk virus</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Fecal-oral</td>
<td>2-4 d ±</td>
<td>– – – ±</td>
<td>3-8 d</td>
<td>None</td>
<td>Can cause severe dehydration Virtually all children are infected by 3 yr of age Oral vaccine given at 2 and 4 mo of age</td>
</tr>
</tbody>
</table>

Traveller’s Diarrhea

- see Acute Diarrhea, ID10

Epidemiology
- most common illness to affect travellers
- up to 50% of travellers to developing countries affected in first 2 wk and 10-20% after returning home

Etiology
- bacterial (80-90%): E. coli most common (ETEC), Campylobacter, Shigella, Salmonella, Vibrio (non-cholera); wide regional variation (e.g. Campylobacter more common in Southeast Asia)
- viral: norovirus, rotavirus, and astrovirus account for 5-8% * protozoal (rarely): Giardia, Entamoeba histolytica, Cryptosporidium, and Cyclospora for ~10% in long-term travellers
- pathogen-negative traveller’s diarrhoea common despite exhaustive microbiological workup

Treatment
- rehydration is the mainstay of therapy
  - rehydrate with sealed beverages
  - in severe fluid loss use oral rehydration solutions (1 package in 1 L boiled or treated water)
- treat symptoms: anti diarrheal agents (e.g. bismuth salicylate, loperamide)
- empiric antibiotics in moderate or severe illness: ciprofloxacin or azithromycin or rifaximin
- note: there is increasing fluoroquinolone resistance in causative agents, especially in Southeast Asia

Prevention
- proper hygiene practices
  - avoid consumption of: foods or beverages from establishments with unhygienic conditions (e.g. street vendors), raw fruits or vegetables without a peel, raw or undercooked meat and seafood
  - avoid untreated water
- bismuth salicylate (Pepto-Bismol®): 60% effective (2 tablets qid according to CDC website)
- CDC Guidelines: antibiotic prophylaxis not recommended
- increased risk of infection with resistant organisms
- high risk groups (e.g. immunocompromised) likely to be infected with pathogen not covered by standard antimicrobial agents

Bismuth salicylate (Pepto-Bismol®) can cause patients to have black stools, which may be mistaken for melena
• Dukoral®: oral vaccine that offers protection against *V. cholerae* (efficacy ~80%) and ETEC (efficacy ~50-67%). Not recommended for routine use in travellers, but the PHAC recommends that it may be considered in short-term travellers >2 yr old who are high-risk (e.g. chronic illness) for whom there is an increased risk of serious consequences for traveller’s diarrhea (e.g. chronic renal failure, CHF, type 1 DM, inflammatory bowel disease), immunosuppressed, history of repeat traveller’s diarrhea, increased risk of acquiring traveller’s diarrhea (gastric hypochlorhydria or young children >2 yr), or travellers to cholera endemic countries at increased risk of exposure.

### Chronic Diarrhea
- see Gastroenterology, G16

### Peptic Ulcer Disease *(H. pylori)*
- see Gastroenterology, G12

### Bone and Joint Infections

#### Septic Arthritis

**Routes of Infection**
- hematogenous
- contiguous osteomyelitis common in children
- direct inoculation via skin/trauma
- iatrogenic (surgery, arthroscopy, arthrocentesis)

**Etiology**
- gonococcal
  - *N. gonorrhoeae*: previously accounted for 75% of septic arthritis in young sexually active adults
- non-gonococcal
  - *S. aureus*: affects all ages, rapidly destructive, accounts for most non-gonococcal cases of septic arthritis in adults (especially in those with rheumatoid arthritis)
  - *Streptococcus* species (Group A and B)
  - Gram-negatives: affect neonates, elderly, IV drug users, immunocompromised
  - *S. pneumoniae*: affects children
  - *Kingella kingae*: affects children aged <2 yr of age
  - *Haemophilus influenzae* type B (Hib) now rare due to Hib vaccine: consider in unvaccinated children
  - *Salmonella* spp.: characteristic of sickle cell disease
  - coagulase-negative *Staphylococcus* species: prosthetic joints
  - if culture negative: partially-treated infection (prior to oral antibiotics), reactive arthritis, rheumatic fever, less common bacterial causes such as *Borrelia* spp. (Lyme disease) or *Tropheryma whipplei* (Whipple’s disease), and non-infectious causes

**Risk Factors**
- gonococcal
  - age (<40 yr), multiple partners, unprotected intercourse, MSM
- non-gonococcal
  - most affected children are previously healthy with no risk factors: occasionally preceding history of minor trauma
  - bacteremia (extra-articular infection with hematogenous seeding, endocarditis)
  - prosthetic joints/recent joint surgery
  - underlying joint disease (rheumatoid arthritis, osteoarthritis)
  - immunocompromise (DM, chronic kidney disease, alcoholism, cirrhosis)
  - loss of skin integrity (cutaneous ulcer, skin infection)
  - age >80 yr

**Clinical Features of Gonococcal Arthritis**
- two forms (although often overlap)
  - bacteremic form
    - systemic symptoms: fever, malaise, chills
    - gonococcal triad: migratory polyarthralgias, tenosynovitis, dermatitis (pustular skin lesions)
  - septic arthritis form
    - local symptoms in involved joint: swelling, warmth, pain, inability to bear weight, marked decrease in range of motion (see Rheumatology, RH3 for differential diagnosis)

**Clinical Features of Non-Gonococcal Arthritis**
- acute onset of pain, swelling, warmth, decreased range of motion ± fever and chills
- most often in large weight-bearing joints (knee, hip, ankle) and wrists
- usually monoarticular (polyarticular risk factors: rheumatoid arthritis, endocarditis, GBS)

### Medical Emergency
Septic arthritis is a medical emergency! If untreated, rapid joint destruction will occur.

### Disseminated Gonococcal Infection Triad
- Migratory arthralgias
- Tenosynovitis next to inflamed joint
- Pustular skin lesions
Investigations
- consider rheumatologic causes for monoarthritis (see Rheumatology, RH3)
- gonococcal: blood C&S, as well as endocervical, urethral, rectal, and oropharyngeal testing
- non-gonococcal: blood C&S
- arthrocentesis (synovial fluid analysis) is mandatory: CBC and differential, Gram stain, C&S, examine for crystals
  - infectious = opaque, increased WBCs (>15,000/mm³: likelihood of infection increases with increasing WBCs), PMNs >90%, culture positive
  - growth of N. gonorrhoeae from synovial fluid is successful in <50% of cases
- ± plain x-ray: assess for osteomyelitis, provides baseline to monitor treatment

Treatment
- medical
  - empiric IV antibiotics: specific choice depends on clinical scenario; for most adults, vancomycin + ceftriaxone is reasonable; for fully vaccinated children, cefazolin or clonacillin IV unless MRSA is a consideration – delay may result in joint destruction
  - Gram stain and cultures guide subsequent treatment
  - gonococcal: ceftriaxone + azithromycin, for concurrent treatment of C. trachomatis
  - non-gonococcal: antibiotics against Streptococcus spp. (2-3 wk IV f/b PO), S. aureus (4 wk IV minimum), or GNB (4 wk)
- surgical drainage if (see Orthopedics, OR10)
  - persistent positive joint cultures on repeat arthrocentesis
  - hip joint involvement
  - prosthetic joint
- daily joint aspirations until culture sterile; no need to give intra-articular antibiotics
- physiotherapy

Prognosis
- gonococcal: responds well after 24-48 h of initiating antibiotics (usually complete recovery)
- non-gonococcal: in children, generally good outcome if treated promptly; in adults, up to 50% morbidity (decreased joint function/mobility)

Diabetic Foot Infections
Etiology
- neuropathy, peripheral vascular disease, and hyperglycemia contribute to foot ulcers that heal poorly, and are predisposed to infection
- organisms in mild infection: S. aureus, Streptococcus spp.
- organisms in moderate/severe infection: polymicrobial with aerobes (S. aureus, Streptococcus, Enterococcus, GNB) and anaerobes (Peptostreptococcus, Bacteroides, Clostridium)

Clinical Features
- not all ulcers are infected
- consider infection if: probe to bone (see below), ulcer present >30 d, recurrent ulcers, trauma, PVD, prior amputation, loss of protective sensation, renal disease, history of walking barefoot
- diagnosis of infected ulcer: ≥2 of the cardinal signs of inflammation (redness, warmth, swelling, pain) or the presence of pus
- ± crepitus, osteomyelitis, systemic toxicity
- visible bone or probe to bone → osteomyelitis
- infection severity
  - mild = superficial (no bone/joint involvement)
  - moderate = deep (beneath superficial fascia, involving bone/joint) or erythema >2 cm
  - severe = infection in a patient with systemic toxicity (fever, tachypnea, leukocytosis, tachycardia, hypotension)

Investigations
- curettage specimen from ulcer base, aspirate from an abscess or bone biopsy (results from superficial swabs do not represent organisms responsible for deeper infection)
- blood C&S if febrile
- assess for osteomyelitis by x-ray (although not sensitive in early stages) or MRI if high clinical suspicion
  - if initial x-ray normal, repeat 2-4 wk after initiating treatment to increase test sensitivity

Treatment
- evaluate for early surgical debridement ± revascularization or amputation
- eliminate/reduce pressure and provide regular local wound care
- mild: cephalaxin or clindamycin
- moderate: clindamycin + ciprofloxacin or moxifloxacin PO, ceftriaxone or ertapenem IV ± MRSA coverage
- severe: piperacillin/tazobactam or meropenem IV ± vancomycin if MRSA known or suspected
- encourage glycemic control

Does this Patient with Diabetes have Osteomyelitis of the Lower Extremity? JAMA 2008;299:906-913
Study: Systematic literature review, 21 studies.
Population: 1,027 adult patients with DM being investigated for osteomyelitis.
Intervention: Various aspects of history, physical exam, laboratory tests, and diagnostic imaging studies versus bone biopsy.
Primary Outcome: Diagnostic utility.
Results: No studies examined any part of history taking. Temperature, ulcer characteristics (erythema, swelling, purulence), elevated WBC, skin swabs, and soft tissue cultures were not useful. Nuclear imaging has poor specificity for osteomyelitis (62%-89.5%), and MRIs have greater accuracy in detecting osteomyelitis.

<table>
<thead>
<tr>
<th>Finding</th>
<th>(+) LR</th>
<th>(-) LR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Visualization of bone</td>
<td>0.2</td>
<td>0.70</td>
<td></td>
</tr>
<tr>
<td>Ulcer area &gt; 2 cm²</td>
<td>1.2</td>
<td>0.48</td>
<td></td>
</tr>
<tr>
<td>Probe-to-bone</td>
<td>6.4</td>
<td>0.39</td>
<td></td>
</tr>
<tr>
<td>Clinical judgment</td>
<td>5.5</td>
<td>0.54</td>
<td></td>
</tr>
<tr>
<td>ESR &gt; 70 mm/h</td>
<td>11</td>
<td>NS*</td>
<td></td>
</tr>
<tr>
<td>Plain radiographs</td>
<td>2.3</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>MRI</td>
<td>3.8</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

*NS = not significant
**Osteomyelitis**
- see Orthopedics, OR10

**Cardiac Infections**

**Infective Endocarditis**

**Definition**
- infection of cardiac endothelium, most commonly the valves
- classifications: acute vs. subacute, native valve vs. prosthetic valve, right sided vs. left sided
- leaflet vegetations are made of platelet-fibrin thrombi, WBCs, and bacteria

**Risk Factors and Etiology**
- predisposing conditions
  - **high risk**: prosthetic cardiac valve, previous IE, congenital heart disease (unrepaired, repaired within 6 mo, repaired with defects), cardiac transplant with valve disease (surgically constructed systemic-to-pulmonary shunts or conduits)
  - **moderate risk**: other congenital cardiac defects, acquired valvular dysfunction, hypertrophic cardiomyopathy
  - **low/no risk**: secundum ASD or surgically repaired ASD < VSD, PDA, MV prolapse, ischemic heart disease, previous CABG
- frequency of valve involvement MV >> AV > TV > PV
  - but in 50% of IVDU-related IE the tricuspid valve is involved

**Table 16. Microbial Etiology of Infective Endocarditis Based on Risk Factors**

<table>
<thead>
<tr>
<th>Native Valve</th>
<th>Intravenous Drug Users (IVDU)</th>
<th>Prosthetic Valve (recent surgery &lt;2 mo)</th>
<th>Prosthetic Valve (remote surgery &gt;2 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptococcus (36%)</td>
<td>S. aureus (68%)</td>
<td>S. aureus (36%)</td>
<td>Streptococcus (20%)</td>
</tr>
<tr>
<td>S. aureus (28%)</td>
<td>Streptococcus (13%)</td>
<td>Other</td>
<td>S. aureus (20%)</td>
</tr>
<tr>
<td>Enterococcus (11%)</td>
<td>GNB</td>
<td>Enterococcus</td>
<td>Other</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>GNB</td>
<td>S. epidermidis (17%)</td>
<td>Other</td>
</tr>
<tr>
<td>GNB</td>
<td>Candida</td>
<td>Other</td>
<td></td>
</tr>
<tr>
<td>Other²</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Organisms in bold are the most common isolates.
1. Streptococcus includes mainly viridans group streptococci
2. Other includes less common organisms such as:
   - Streptococcus pneumoniae (previously known as S. pneumoniae, usually associated with underlying GI malignancy, cirrhosis)
   - Culture-negative organisms including nutritionally-deficient streptococci, HACEK, Bartonella, Coxiella, Chlamydia, Legionella, Brucella
   - Candida
3. IVDU endocarditis pathogens depend on substance used to dilute the drugs (i.e. tap water = Pseudomonas, saliva = oral flora, toilet water = GI flora)

**Clinical Features**
- systemic
  - fever (80-90%), chills, weakness, rigors, night sweats, weight loss, anorexia
- cardiac
  - dyspnea, chest pain, clubbing (subacute)
  - regurgitant murmur (new onset or increased intensity)
  - signs of CHF (secondary to acute MR, AR)
- embolic/vascular
  - petechiae over legs, splinter hemorrhages (linear, reddish-brown lesion within nail bed)
  - Janeway lesions (painless, 5 mm, erythematous, hemorrhagic pustular lesions on soles/palms)
  - focal neurological signs (CNS emboli), H/A (myotic aneurysm)
  - splenomegaly (subacute)
  - microscopic hematuria, flank pain (renal emboli) ± active sediment
- immune complex
  - Osler’s nodes (painful, raised, red/brown, 3-15 mm on digits)
  - glomerulonephritis
  - arthritis
  - Roth’s spots (retinal hemorrhage with pale centre)

**Diagnosis**
- Modified Duke Criteria, see Table 17
  - definitive diagnosis if: 2 major, OR 1 major + 3 minor, OR 5 minor
  - possible diagnosis if: 1 major + 1 minor, OR 3 minor
Table 17. Modified Duke Criteria

**Major Criteria (2)**

1. Positive blood cultures for IE
   - Typical microorganisms for IE from 2 separate blood cultures (Streptococcus viridans, HACEK group (see ID16), Streptococcus gallolyticus (previously known as S. bovis), Staphylococcus aureus, community-acquired enterococci) OR
   - Persistently positive blood culture, defined as recovery of a microorganism consistent with IE from blood drawn >12 h apart OR
   - All of 3 or a majority of 4 or more separate blood cultures, with first and last drawn >1 h apart OR
   - Single positive blood culture for Coxiella burnetii or antiphase IgG antibody titer >1:800

2. Evidence of endocardial involvement
   - Positive echocardiogram for IE (oscillating intracardiac mass on valve or supporting structures, or in the path of regurgitant jets, or on implanted material in the absence of an alternate anatomic explanation OR abscess OR new partial dehiscence of prosthetic valve) OR
   - New valvular regurgitation (insufficient if increase or change in preexisting murmur)

**Minor Criteria (5)**

1. Predisposing condition (abnormal heart valve, IVDU)
2. Fever (38.0°C/100.4°F)
3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, ICH, conjunctival hemorrhages, Janeway lesions
4. Immunologic phenomena: glomerulonephritis, rheumatoid factor, Osler’s nodes, Roth’s spots
5. Positive blood culture but not meeting major criteria OR serologic evidence of active infection with organism consistent with IE

**Investigations**

- serial blood cultures: 3 sets (each containing one aerobic and one anaerobic sample) collected from different sites >1 h apart
  - persistent bacteremia is the hallmark of endovascular infection (such as IE)
- repeat blood cultures (at least 2 sets) after 48 to 72 h of appropriate antibiotics to confirm clearance
- blood work: CBC and differential (normochromic, normocytic anemia), ESR (increased), RF (+), BUN/Cr
- urinalysis (proteinuria, hematuria, red cell casts) and urine C&S
- ECG: prolonged PR interval may indicate perivalvular abscess
- Echo findings: vegetations, regurgitation, abscess
  - TTE (poor sensitivity) inadequate in 20% (obesity, COPD, chest wall deformities)
  - TEE indicated if TTE is non-diagnostic in patients with at least possible endocarditis or if suspect prosthetic valve endocarditis or complicated endocarditis (e.g. paravalvular abscess/perforation) (~90% sensitivity)

**Treatment**

- medical
  - usually non-urgent and can wait for confirmation of etiology before initiating treatment
  - empiric antibiotic therapy if patient is unstable; administer ONLY after blood cultures have been taken
    - first-line empiric treatment for native valve: vancomycin + gentamicin OR ceftriaxone
    - first line empiric treatment for prosthetic valve: vancomycin + gentamicin + cefepime + rifampin
  - targeted antibiotic therapy: antibiotic and duration (usually 4-6 wk) adjusted based on valve, organism, and sensitivities
  - monitor for complications of IE (e.g. CHF, conduction block, new emboli) and complications of antibiotics (e.g. interstitial nephritis)
  - prophylaxis only for high risk individuals listed above with dental procedures that may lead to bleeding OR invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa, such as tonsillectomy and adenoidectomy OR procedures on infected skin, skin structure, or musculoskeletal tissue
    - dental/respiratory: amoxicillin single dose 30-60 min prior; clindamycin if penicillin-allergic
    - skin/soft tissue: cephalexin single dose 30-60 min prior; clindamycin if penicillin-allergic (modify based on etiology of skin/soft tissue infection)
  - surgical
    - most common indication is refractory CHF
    - other indications include: valve ring abscess, fungal etiology, valve perforation, unstable prosthesis, ≥2 major emboli, antimicrobial failure (persistently positive blood cultures), mycotic aneurysm, Streptococci on a prosthetic valve

**Prognosis**

- adverse prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess, embolization, persistent bacteremia, altered mental status prognostic factors: CHF, prosthetic valve infection, valvular/myocardial abscess
- mortality: prosthetic valve IE (25-50%), non-IVDU S. aureus IE (30-45%), IVDU S. aureus or streptococcal IE (10-15%)
Meningitis

- see Pediatrics, P60

Definition
- inflammation of the meninges

Etiology

Table 18. Common Organisms in Meningitis

<table>
<thead>
<tr>
<th>Bacterial</th>
<th>Viral</th>
<th>Fungal</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 0-4 wk</td>
<td>Age 1-23 mo</td>
<td>Age &gt;2 yr</td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>GBS</td>
<td>S. pneumoniae</td>
<td>HSV 1, 2</td>
</tr>
<tr>
<td>E. coli</td>
<td>E. coli</td>
<td>N. meningitidis</td>
<td>VZV</td>
</tr>
<tr>
<td>L. monocytogenes</td>
<td>S. pneumoniae</td>
<td>L. monocytogenes</td>
<td>Enteroviruses</td>
</tr>
<tr>
<td>Klebsiella</td>
<td>N. meningitidis</td>
<td>(age &gt;50 and comorbidities)</td>
<td>Parechoviruses</td>
</tr>
<tr>
<td>H. influenzae</td>
<td></td>
<td></td>
<td>West Nile</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td></td>
<td></td>
<td>Neurosyphilis</td>
</tr>
<tr>
<td>Coccioides</td>
<td></td>
<td></td>
<td>TB</td>
</tr>
<tr>
<td>Lyme disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Risk Factors
- lack of immunization against S. pneumoniae, H. influenzae type b in children
- hematogenous spread after invasion from a mucosal surface (nasopharynx)
- parameningeal focus (otitis media, infection, sinusitis)
- penetrating head trauma
- anatomical meningeal defects – CSF leaks
- previous neurosurgical procedures, shunts
- immunodeficiency (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

Clinical Features
- neonates and children: fever, lethargy, irritability, vomiting, poor feeding
- older children and adults: fever, H/A, neck stiffness, confusion, lethargy, altered level of consciousness, seizures, focal neurological signs, N/V, photophobia, papilledema
- petechial rash in meningococcal meningitis, seen more frequently on trunk or lower extremities

Investigations
- blood work: CBC and differential, electrolytes (for SIADH), blood C&S
- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
- AFB, fungal C&S, cryptococcal antigen in immunocompromised patients, subacute illness, suggestive travel history or TB exposure
- PCR for HSV, VZV, enteroviruses; in infants <6 mo, parechoviruses
- WNV serology in blood and CSF during summer and early fall if viral cause suspected
- Listeria monocytogenes – GN diplococci
- H. influenzae – Pleomorphic GN coccobacilli
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Treatment
- bacterial meningitis is a medical emergency: do not delay antibiotics for CT or LP
- empiric antibiotic therapy
  - age <6 wk: ampicillin + cefotaxime IV OR ampicillin ± an aminoglycoside IV; add vancomycin if suspect S. pneumoniae
  - 6 wks-3 mo: ampicillin + cefotaxime + vancomycin
  - age >3 mo: vancomycin + cefotaxime or ceftriaxone IV
  - add ampicillin IV if risk factors for infection with L. monocytogenes present: age >50, alcoholism, immunocompromised
- steroids in acute bacterial meningitis: dexamethasone IV within 20 min prior to or with first dose of antibiotics
- continue in those patients with proven pneumococcal meningitis
- not recommended for patients with suspected bacterial meningitis in some resource-limited countries
- not recommended for neonatal meningitis

Risk Factors
- lack of immunization against S. pneumoniae, H. influenzae type b in children
- hematogenous spread after invasion from a mucosal surface (nasopharynx)
- parameningeal focus (otitis media, infection, sinusitis)
- penetrating head trauma
- anatomical meningeal defects – CSF leaks
- previous neurosurgical procedures, shunts
- immunodeficiency (corticosteroids, HIV, asplenia, hypogammaglobulinemia, complement deficiency)
- contact with colonized or infected persons

Clinical Features
- neonates and children: fever, lethargy, irritability, vomiting, poor feeding
- older children and adults: fever, H/A, neck stiffness, confusion, lethargy, altered level of consciousness, seizures, focal neurological signs, N/V, photophobia, papilledema
- petechial rash in meningococcal meningitis, seen more frequently on trunk or lower extremities

Investigations
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- CSF: opening pressure, cell count + differential, glucose, protein, Gram stain, bacterial C&S
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- not recommended for patients with suspected bacterial meningitis in some resource-limited countries
- not recommended for neonatal meningitis
Prevention
• see Pediatrics, P3
• immunization
  ♦ children: immunization against H. influenzae type B (Pentacel®), S. pneumoniae (Synflorix®, Prevnar-13®), N. meningitidis (Menjugate®, Menactra®, Bexsero®)
  ♦ adults: immunization against N. meningitidis in selected circumstances (outbreaks, travel, epidemics) and S. pneumoniae (Pneumovax®) for high-risk groups
• prophylaxis: close contacts of patients infected with H. influenzae type B should be treated with rifampin if they live with an inadequately immunized (<4 yr) or immunocompromised child (<18 yr); ciprofloxacin, rifampin, or ceftriaxone if close or household contact of a patient with N. meningitidis

Prognosis
• complications
  • H/A, seizures, cerebral edema, hydrocephalus, SIADH, residual neurological deficit (especially CN VIII), deafness, death
• mortality
  • S. pneumoniae 25%; N. meningitidis 5-10%; H. influenzae 5%
• worse prognosis if: extremes of age, delays in diagnosis and treatment, stupor or coma, seizures, focal neurological signs, septic shock at presentation

Encephalitis

Definition
• inflammation of the brain parenchyma

Etiology
• identified in only 40-70% of cases
  • when cause is identified, the most common etiology is viral: HSV, VZV, EBV, CMV, enteroviruses, West Nile, HIV, mumps, measles, rabies, polio
  • bacteria: L. monocytogenes, Mycobacteria, spirochetes (Lyme, syphilis), Mycoplasma pneumoniae
  • parasites: protozoa (e.g. Toxoplasma) and helminths (rare)
  • fungi: e.g. Cryptococcus
  • post-infectious (e.g. acute disseminated encephalomyelitis [ADEM])
  • auto-antibody mediated encephalitis
    • anti-N-methyl-D-aspartate (NMDA) receptor encephalitis most common
    • in adults, most autoantibody-mediated encephalitis cases are associated with malignancy

Pathophysiology
• acute inflammatory disease of the brain due to direct invasion or pathogen-initiated immune response
• viruses may reach the CNS via peripheral nerves (e.g. rabies, HSV)
• herpes simplex encephalitis
  • acute, necrotizing, asymmetrical hemorrhagic process with lymphocytic and plasma cell reaction which usually involves the medial temporal and inferior frontal lobes
  • associated with HSV-1, but can also be caused by HSV-2
• influenza and other respiratory viruses are associated with acute necrotizing encephalopathy (ANE); likely mediated by pathogen-initiated immune response

Clinical Features
• constitutional: fever, chills, malaise, N/V
• meningeval involvement (meningoencephalitis): H/A, nuchal rigidity
• parenchymal involvement: seizures, altered mental status, focal neurological signs
• herpes simplex encephalitis
  • acute onset (<1 wk) of focal neurological signs: hemiparesis, ataxia, aphasia, focal or generalized seizures
  • temporal lobe involvement: behavioural disturbance
  • usually rapidly progressive over several days and may result in coma or death
  • common sequelae: memory and behavioural disturbances

Investigations
• CSF: opening pressure, cell count and differential, glucose, protein, Gram stain, bacterial C&S, PCR for HSV, VZV, EBV, enteroviruses/parechoviruses, S. pneumoniae, and selectively for other less common etiologies
• serology: may aid diagnosis of certain causes of encephalitis (e.g. EBV, West Nile virus, rabies, Bartonella henselae)
• imaging/neurologic studies: CT, MRI, EEG to define anatomical sites affected

Meningitis and encephalitis patients can be distinguished based on their cerebral function. Cerebral function is abnormal in encephalitis patients (e.g. altered mental status, motor or sensory deficits, altered behaviour, speech or movement disorders), but may be normal in patients with meningitis. Note however, that there is considerable overlap between the two syndromes (“meningoencephalitis”)
• invasive testing: brain tissue biopsy may be required for culture, histological examination, and immunocytochemistry (if diagnosis not clear via non-invasive means)
  • findings in herpes simplex encephalitis (must rule out due to high mortality)
    ▪ CT/MRI: medial temporal lobe necrosis
    ▪ EEG: early focal slowing, periodic discharges

Treatment
• general supportive care
• monitor vital signs carefully
• IV acyclovir empirically until HSV encephalitis ruled out

Generalized Tetanus

• see Pediatrics, P4

Etiology and Pathophysiology
• caused by Clostridium tetani: motile, spore forming, anaerobic GP bacillus
• found in soil, splinters, rusty nails, GI tract (humans and animals)
• traumatic implantation of spores into tissues with low oxygenation (e.g. puncture wounds, burns, nonsterile surgeries or deliveries)
• upon inoculation, spores transform into C. tetani bacilli that produce tetanus toxin
  ▪ toxin travels via retrograde axonal transport to the CNS where it irreversibly binds presynaptic neurons to prevent the release of inhibitory neurotransmitters (e.g. GABA)
  ▪ net effect is the disinhibition of spinal motor reflexes which results in tetany and autonomic hyperactivity

Clinical Features
• generalized tetanus
  ▪ initially present with painful spasms of masseters (trismus or "lockjaw")
  ▪ sustained contraction of skeletal muscle with periodic painful muscle spasms (triggered by sensory stimuli, e.g. loud noises)
  ▪ paralysis descends to involve large muscle groups (neck, abdomen)
  ▪ apnea, respiratory failure, and death secondary to tonic contraction of pharyngeal and respiratory muscles
• autonomic hyperactivity
  ▪ diaphoresis, tachycardia, HTN, fever as illness progresses

Investigations
• primarily a clinical diagnosis, often although not always with a history of a traumatic wound and lack of immunization
• culture wounds, CK may be elevated

Treatment
• stop toxin production
  ▪ wound debridement to clear necrotic tissue and spores
  ▪ antimicrobial therapy: IV metronidazole; IV penicillin G is an effective alternative
  ▪ neutralize unbound toxin with tetanus immune globulin (TIG)
  ▪ supportive therapy: intubation, spasmylytic medications (benzodiazepines), quiet environment, cooling blanket
  ▪ control autonomic dysfunction: α- and β-blockade (e.g. labetalol), magnesium sulfate

Prevention
• infection with C. tetani does not produce immunity – vaccinate patients on diagnosis
• tetanus toxoid vaccination (see Pediatrics, P4 and Emergency Medicine, ER17)

Rabies

Definition
• acute progressive encephalitis caused by RNA virus (genus Lyssavirus of the Rhabdoviridae family)

Etiology and Pathophysiology
• any mammal can transmit the rabies virus
  ▪ most commonly transmitted by raccoon, skunk, bat, fox, cat, and dog; monkeys also a risk in the developing world
  ▪ transmission: breaching of skin by teeth or direct contact of infectious tissue (saliva, neural tissue) with skin or mucous membranes
  ▪ almost all cases due to bites
  ▪ virus travels via retrograde axonal transport from PNS to CNS
  ▪ virus multiplies rapidly in brain, then spreads to other organs, including salivary glands
  ▪ development of clinical signs occurs simultaneously with excretion of rabies virus in saliva
    ▪ infected animal can transmit rabies virus as soon as it shows signs of disease
Clinical Features
• five stages of disease
  1. incubation period
     • 1-3 mo on average (can range from days to years)
  2. prodrome (<1 wk)
     • influenza-like illness: low-grade fever, malaise, anorexia, N/V, H/A, sore throat
     • pain, pruritus, and paresthesia may occur at wound site
     • once prodromal symptoms develop, there is rapid, irreversible progression to death
       • progression from prodrome to coma and death may occur without an intervening acute
         neurologic syndrome
  3. acute neurologic syndrome: 3 types (<1 wk)
     a. encephalitic (most common): hyperactivity, fluctuating LOC, hydrophobia, aerophobia,
        hypersalivation, fever, seizures
        • painful pharyngeal spasms on encountering gust of air or swallowing water cause
        aerophobia and hydrophobia, respectively
     b. paralytic: quadriplegia, loss of anal sphincter tone, fever
     c. atypical: rare
  4. coma
     • complete flaccid paralysis, respiratory and cardiovascular failure
  5. death (within days to weeks of initial symptoms)

Investigations
• purpose of diagnosis by investigations is to limit patient contact with others and to identify
  others exposed to the infectious source
• ante-mortem: direct immunofluorescence or PCR on multiple specimens: saliva, skin biopsy,
  serum, CSF
• post-mortem: direct immunofluorescence in nerve tissue, presence of Negri bodies (inclusion
  bodies in neurons)

Treatment
• post-exposure prophylaxis depends on regional prevalence (contact Public Health) and
  circumstances surrounding injury
• 3 general principles
  • wound care: clean wound promptly and thoroughly with soap and running water
  • passive immunization: HRIg infiltrated into wound site, with any remaining volume
    administered IM in anatomical site distant from vaccine administration
  • active immunization: inactivated human diploid cell rabies virus vaccine (series of 4 shots
    post-exposure if not pre-immunized)
• treatment is supportive once victim manifests signs and symptoms of disease

Prevention
• pre-exposure vaccination
  • recommended for high risk persons: laboratory staff working with rabies, veterinarians,
    animal and wildlife control workers, long-term travellers to endemic areas
  • eliminates need for HRIg following an exposure, and reduces number of HDCV PEP shots
    from 4 to 2

Systemic Infections

Sepsis and Septic Shock
• see Respirology, R33

Definitions
• systemic inflammatory response syndrome (SIRS): 2 or more of
  1. temperature <36°C/96.8°F or >38°C/100.4°F
  2. heart rate >90 beats/min
  3. respiratory rate >20 breaths/min or PaCO₂ <32 mmHg
  4. WBC <4 x 10⁹/L or >12 x 10⁹/L or >10% bands
• severe sepsis: SIRS + signs of end-organ dysfunction and hypoperfusion
• septic shock: severe sepsis + hypotension (<90 mmHg sBP), despite adequate fluid resuscitation

Pathophysiology
• causative agents are identified in only 50-70% of cases
• when organisms are identified, GP and GN organisms are the cause in 90% of cases
• primary bloodstream infection or secondary bacteremia → local immune response → immune
  cells release pro-inflammatory cytokines → immune response spreads beyond local environment
  → unregulated, exaggerated systemic immune response → vasodilation and hypotension →
  involvement of tissues remote from the site of injury/infection resulting in multiple major organ
dysfunction → periodic immunoparalysis
Clinical Features
- history: fever, chills, dyspnea, cool extremities, fatigue, malaise, anxiety, confusion
- physical: abnormal vitals (fever, tachypnea, tachycardia, hypotension), local signs of infection

Investigations
- CBC and differential, electrolytes, BUN, creatinine, liver enzymes, ABG, lactate, INR, PTT, FDP, blood C&S x2, urinalysis, urine C&S and cultures of any wounds or lines
- CXR (other imaging depends on suspicion of focus of infection)

Treatment
- respiratory support: O₂ ± intubation
- cardiovascular support: IV fluids, ± norepinephrine + ICU
- IV antibiotics (empirical, depends on suspected source)
  - start with broad spectrum antibiotics (piperacillin/tazobactam or meropenem) ± additional agents depending on patient risk factors, suspected etiology of infection, and local microbial susceptibilities (± aminoglycoside for drug-resistant GNS or vancomycin for MRSA)
  - narrow once susceptibilities are known
- hydrocortisone IV in patients with septic shock unresponsive to fluid resuscitation and vasopressors

Leprosy (Hansen’s Disease)

Etiology
- Mycobacterium leprae: obligate intracellular bacteria, slow-growing (doubling time 12.5 d), survives in macrophages
- bacteria transmitted from nasal secretions, potentially via skin lesions
- invades skin and peripheral nerves leading to chronic granulomatous disease

Clinical Features
- lesions involve cooler body tissues (e.g. skin, superficial nerves, nose, eyes, larynx)
- spectrum of disease determined by host immune response to infection
  i. paucibacillary “tuberculoid” leprosy (intact cell-mediated immune response)
     - ≤5 hypoesthetic lesions, usually hypopigmented, well-defined, dry
     - early nerve involvement, enlarged peripheral nerves, neuropathic pain
     - may be self-limited, stable, or progress over time to multibacillary "lepromatous" form
  ii. multibacillary "lepromatous" leprosy (weak cell-mediated immune response)
     - ≥6 lesions, symmetrical distribution
     - leonine facies (nodular facial lesions, loss of eyebrows, thickened ear lobes)
     - extensive cutaneous involvement, late and insidious nerve involvement causing sensory loss at the face and extremities
  iii. borderline leprosy
     - lesions and progression lies between tuberculoid and lepromatous forms

Investigations
- skin biopsy down to fat or slit skin smears for AFB staining, PCR
- histologic appearance: intracellular bacilli in spherical masses (lepra cells), granulomas involving cutaneous nerves

Treatment (WHO Treatment Regimens)
- paucibacillary: dapsone + rifampin monthly x 6 mo
- single skin lesion paucibacillary: single dose of rifampin, ofloxacin, and minocycline
- multibacillary and borderline: dapsone + rifampin monthly + clofazimine monthly x 12 mo
  AND low dose clofazimine once daily x 12 mo
- treatment of leprosy can cause an immune reaction to killed bacteria (e.g. erythema nodosum leprosum and reversal reaction): symptomatic management with NSAIDs if mild, prednisone with 6-12 wk taper if severe; thalidomide for erythema nodosum leprosum

Prognosis
- curable with WHO-approved treatment regimens
- complications: muscle atrophy, contractures, trauma/superinfection of lesions, crippling/loss of limbs, erythema nodosum leprosum, social stigmatization due to clofazimine hyperpigmentation
- long post-treatment follow-up warranted to monitor for relapse and immune reactions
Lyme Disease

Etiology/Epidemiology
- spirochete bacteria: *Borrelia burgdorferi* (N. America), *B. garinii*, *B. afzelii* (Europe and Asia)
- transmitted by *Ixodes* tick
- reported in 49 of the 50 U.S. states, but most cases occur in the Northeast, the Midwest, and Northern California
- in Canada, reported in southern and southeastern Quebec, southern and eastern Ontario, southeastern Manitoba, New Brunswick and Nova Scotia, as well as southern British Columbia
- small rodents (mice) serve as primary reservoir, while larger animals (white-tailed deer) serve as hosts for ticks
- human contact usually May-August in fields with low brush near wooded areas
- infection usually requires >36 h tick attachment

Clinical Features
- stage 1 (early localized stage: 7-14 d post-bite)
  - malaise, fatigue, H/A, myalgias
  - erythema migrans: expanding, non-pruritic bulls-eye (target) lesions (red with clear centre) on thigh/groin/axilla
- stage 2 (early disseminated stage): weeks post-infection
  - CNS: aseptic meningitis, CN palsies (CN VII palsy), peripheral neuritis
  - cardiac: transient heart block or myocarditis
- stage 3 (late persistent stage: months to years post-infection)
  - may not have preceding history of early stage infection
  - MSK: chronic monoarticular or oligoarticular arthritis
  - acrodermatitis chronicum atrophicans (due to *B. afzelii*)
  - neurologic: encephalopathy, meningitis, neuropathy

Investigations
- serology: ELISA, Western blot

Prevention
- use of protective clothing (tuck pants into socks), insect repellent, inspection for ticks and prompt removal of tick
- doxycycline prophylaxis within 72 h of removal of an engorged, *Ixodes scapularis* tick in hyperendemic area (local rate of infection of ticks ≥20%) for patients >8 yr who are not pregnant or lactating

Treatment
- stage 1: doxycycline/amoxicillin/cefuroxime
- stage 2-3: ceftriaxone

Toxic Shock Syndrome

Etiology
- superantigens produced by some strains of *S. aureus* or GAS cause widespread T-cell activation and pro-inflammatory cytokine release (IL-1, IL-6, TNF)
- course of disease is precipitous and leads to acute fever, shock, multiorgan failure
- Staphylococcal TSS involves the production of superantigen TSST-1 (toxic shock syndrome toxin 1)
- Streptococcal TSS involves the production of superantigens SPEA, SPEB, SPEC

Risk Factors
- Staphylococcal: tampon use, nasal packing, wound infections (e.g. postpartum vaginal or Cesarean or other surgical infections)
- Streptococcal: minor trauma, surgical procedures, preceding viral illness (e.g. chickenpox), use of NSAIDs

Clinical Features and Investigations
- acute onset
- Staphylococcal TSS
  - T >38.9°C
  - sBP <90 mmHg
  - diffuse erythroderma with subsequent desquamation, especially on palms and soles
  - involvement of 3 or more organ systems: GI (vomiting, diarrhea), muscular (myalgia, increased CK), mucous membranes (hyperemia), renal, hepatic, hematologic (thrombocytopenia), CNS (disorientation)
  - isolation of *S. aureus* is not required for diagnosis (*S. aureus* is rarely recovered from blood in TSS)
• Streptococcal TSS
  ▪ sBP <90 mmHg
  ▪ isolation of GAS from a normally sterile site (e.g. blood, pleural, tissue biopsy, or surgical wound)
  ▪ ≥2 of coagulopathy, liver involvement, ARDS, soft tissue necrosis (necrotizing fasciitis, myositis, gangrene), renal impairment, erythematous macular rash that may desquamate

Treatment
• supportive: fluid resuscitation
  ▪ Staphylococcal: for methicillin-susceptible S. aureus: clindamycin + cloxacillin (IV); for MRSA: clindamycin + vancomycin x 10-14 d
  ▪ Streptococcal: IV penicillin and clindamycin and ± IVIg

Cat Scratch Disease

Etiology
• Bartonella henselae: intracellular bacteria
• cat-to-human transmission via cat scratch/bite

Clinical Features
• skin lesion appears 3-10 d post-inoculation
• may be followed by fever, tender regional lymphadenopathy
• in some patients, organism may disseminate causing fever of unknown origin, hepatosplenomegaly, retinitis, encephalopathy
• usually self-limited

Investigations
• serology, PCR, lymph node biopsy

Treatment
• supportive in most cases
• azithromycin x 10-14 d with lymphadenitis in patients with moderate-severe disease or immunodeficiency

Rocky Mountain Spotted Fever

Etiology
• Rickettsia rickettsii: obligate intracellular GN organism
• reservoir hosts: rodents, dogs
• vectors: Dermacentor ticks
• organisms cause inflammation of endothelial lining of small blood vessels, leading to small hemorrhages and thrombi
• can cause widespread vasculitis leading to H/A, and CNS changes; can progress to death if treatment is delayed

Clinical Features
• usually occurs in summer following tick bite
• influenza-like prodrome: acute onset fever, H/A, myalgia, N/V, anorexia
• macular rash appearing on day 2-4 of fever
  ▪ begins on wrists and ankles, then spreads centrally to arms/legs/trunk/palms/soles
  ▪ occasionally “spotless” (10% of patients)

Investigations
• skin biopsy and serology (indirect fluorescent antibody test)

Treatment
• doxycycline, usually 5-7 d (treat for 3 d after defervescence)

West Nile Virus

Epidemiology
• virus has been detected throughout the United States and much of southern Canada
• overall case-fatality rates in severe cases are ~10%

Transmission
• primarily from mosquitoes that have fed on infected birds (crows, blue jays)
• transplacental, blood products (rare), organ transplantation
Clinical Features
- most are asymptomatic
- most symptomatic cases are mild (West Nile fever): acute onset of H/A, back pain, myalgia, anorexia, maculopapular non-pruritic rash involving chest, back, arms
- severe complications: encephalitis, meningoencephalitis, and acute flaccid paralysis (especially in those >60 yr)

Investigations
- IgM antibody in serum or CSF (cross reactivity with yellow fever and Japanese encephalitis vaccines, and with dengue fever and St. Louis virus infection); may not reflect current illness as IgM antibody can last for >6 mo
- viral isolation by PCR from CSF, tissue, blood, and fluids (all have low sensitivity)
- CSF: elevated lymphocytes and protein if CNS involvement

Treatment and Prevention
- treatment: supportive
- prevention: mosquito repellant (DEET), drain stagnant water, community mosquito control programs

Syphilis

Etiology
- Treponema pallidum: thick motile spirochetes historically detectable by dark-field microscopy
- transmitted sexually, vertically, or parenterally (rare)

Clinical Features
- see Dermatology, D32 and Gynecology, GY30
- multi-stage disease
  1. primary syphilis (3-90 d post-infection)
     - painless chancre at inoculation site (any mucosal surface)
     - regional lymphadenopathy
     - acute disease lasts 3-6 wk, 25% progress to secondary syphilis without treatment
  2. secondary syphilis = systemic infection (2-8 wk following chancre)
     - maculo-papular non-pruritic rash including palms and soles
     - generalized lymphadenopathy, low grade fever, malaise, H/A, aseptic meningitis, ocular/otic syphilis
     - condylomata lata: painless, wart-like lesion on palate, vulva, or scrotum (highly infectious)
  3. latent syphilis
     - asymptomatic infection that follows untreated primary/secondary syphilis
     - early latent (<1 yr post-infection) or late latent/unknown duration (>1 yr post-infection)
     - increased transmission risk with early latent; longer treatment duration required for late latent
  4. tertiary syphilis (1-30 yr post-infection)
     - gummatous syphilis: nodular granulomas of skin, bone, liver, testes, brain
     - aortic aneurysm and aortic insufficiency
     - neurosyphilis: dementia, personality changes, Argyll-Robertson pupils, tabes dorsalis
  5. congenital syphilis
     - causes spontaneous abortions, stillbirths, congenital malformations, developmental delay, deafness
     - most infected newborns are asymptomatic
     - clinical manifestation in early infancy include rhinitis (sniffles), lymphadenopathy, hepatosplenomegaly, pseudoparalysis (bone pain associated with osteitis)
     - late onset manifestations (>2 yr of age) include saddle nose, saber shins, joint deformities, Hutchinson’s teeth, mulberry molars, ragades, CN VIII deafness, interstitial keratitis, juvenile paresis

Investigations
- screening tests: CMIA, CLIA, EIA (treponemal), RPR, or VDRL (non-treponemal)
- confirmatory tests: TPPA, FTA-ABS, MHA-TP, TPI, dark field microscopy with silver stain (rarely)
- LP for neurosyphilis if: seropositive and symptoms of neurosyphilis or treatment failure/other tertiary symptoms, or with HIV and late latent/unknown duration syphilis; consider in others
- for congenital syphilis, LP is essential; long bone x-rays may also be helpful

Treatment
- for 1st, 2nd, early latent: benzathine penicillin G 2.4 million units IM x 1
- for 3rd, late latent: benzathine penicillin G 2.4 million units IM weekly x 3
- if allergic to penicillin: doxycycline 100 mg PO bid x 14 d
- neurosyphilis: aqueous Penicillin G 18-24 million units/d IV x 14 d
- for congenital syphilis, penicillin G IV x 10 d
- see Family Medicine, FM45 for generalized STI workup
Tuberculosis

Etiology, Epidemiology, and Natural History

- 1/3 of the world’s population is infected with TB
- contracted by aerosolized inhalation of *Mycobacterium tuberculosis*, a slow growing aerobe (doubling time = 18 h) that can evade innate host defenses, survive, and replicate in macrophages
- inhalation and deposition in the lung can lead to one of the following outcomes
  1. immediate clearance of the pathogen
  2. latent TB: asymptomatic infection contained by host immune defenses (represents 95% of infected people)
  3. primary TB: symptomatic, active disease (represents 5% of infected people)
  4. secondary TB: symptomatic reactivation of previously dormant TB (represents 5-10% of those with latent TB, most often within the first 2-3 yr of initial infection) at a pulmonary or extrapulmonary site

Figure 8. Tuberculosis statistics

Canadian Tuberculosis Standards, 7th ed.

Risk Factors

- social and environmental factors
  - travel or birth in a country with high TB prevalence (e.g. Asia, Latin America, Sub-Saharan Africa, Eastern Europe)
  - Aboriginal (particularly Inuit), crowded living conditions, low SES/homeless, IVDU
  - personal or occupational contact
- host factors
  - immunocompromised/immunosuppressed (especially HIV, including extremes of age)
  - silicosis
  - chronic renal failure requiring dialysis
  - malignancy and chemotherapy
  - substance abuse (e.g. drug use, alcoholism, smoking)

Clinical Features

- primary infection usually asymptomatic, although progressive primary disease may occur, especially in children and immunosuppressed patients
- secondary infection/reactivation usually produces constitutional symptoms (fatigue, anorexia, night sweats, weight loss) and site-dependent symptoms
  1. pulmonary TB
    - chronic productive cough ± hemoptysis
    - CXR consolidation or cavitation, lymphadenopathy
    - non-resolving pneumonia despite standard antimicrobial therapy
  2. miliary TB
    - widely disseminated spread especially to lungs, abdominal organs, marrow, CNS
    - CXR: multiple small 2-4 mm millet seed-like lesions throughout lung
  3. extrapulmonary TB
    - lymphadenitis, pleurisy, pericarditis, hepatitis, peritonitis, meningitis, osteomyelitis (vertebral = Pott’s disease), adrenal (causing Addison’s disease), renal, ovarian

Tuberculous Polyserositis
pleural + pericardial + peritoneal effusions (usually from granuloma breakdown that spills TB into pleural cavity – very rare)
**Investigations**
- screening for latent TB
  - PPD/Mantoux skin tests
    - both tests diagnose prior TB exposure; neither can diagnose or exclude active disease
  - IFN-γ release assay (IGRA)
    - in patients previously infected with TB, T-cells produce increased amounts of IFN-γ when re-exposed to TB antigen
    - detects antigen not present in the BCG vaccine or in most types of non-tuberculous-mycobacteria (NTM), therefore fewer false positives
- Canadian and American guidelines treat IGRA as equivalent to the TB skin test and preferable in patients with a history of BCG vaccination or who may not return for a skin test reading
- diagnostic tests/investigations for active pulmonary TB
  - three sputum specimens (either spontaneous or induced) should be collected for acid-fast bacilli smear and culture; the three specimens can be collected on the same day, a minimum of 1 hour apart
  - BAL
  - CXR
    - nodular or alveolar infiltrates with cavitation (middle/lower lobe if primary, apical if secondary)
    - pleural effusion (usually unilateral and exudative) may occur independently of other radiograph abnormalities
    - hilar/mediastinal adenopathy (especially in children)
    - tuberculoma (semi-calcified well-defined solitary coin lesion 0.5-4 cm that may be mistaken for lung CA)
    - miliary TB
    - evidence of past disease: calcified hilar and mediastinal nodes, calcified pulmonary focus, pleural thickening with calcification, apical scarring

**Prevention**
- primary prevention
  - airborne isolation for active pulmonary disease
  - BCG vaccine
    - ~80% effective against pediatric miliary and meningeal TB
    - effectiveness in adults debated (anywhere from 0-80%)
    - recommended in high-incidence communities in Canada for infants in whom there is no evidence of HIV infection or immunodeficiency; widely used in other countries
- secondary prevention (defer in pregnancy unless mother is high risk)
  - likely INH-sensitive: isoniazid (INH) + pyridoxine (vit B6 to help prevent INH-associated neuropathy) x 9 mo
  - likely INH-resistant: rifampin x 4 mo

**Treatment of Active Infection**
- empiric therapy: INH + rifampin + pyrazinamide + ethambutol + pyridoxine
- pulmonary TB: INH + rifampin + pyrazinamide + ethambutol + pyridoxine x 2 mo (initiation phase), then INH + rifampin + pyridoxine x 4 mo in fully susceptible TB (continuation phase), total 6 mo
- extrapulmonary TB: same regimen as pulmonary TB but increase to 12 mo in bone/joint, CNS, and miliary/disseminated TB + corticosteroids for meningitis, pericarditis
- empiric treatment of suspected MDR (multidrug resistant) or XDR (extensively drug-resistant) TB requires referral to a specialist
  - MDR = resistance to INH and rifampin ± others
  - XDR = resistance to INH + rifampin + fluoroquinolone + ≥1 of injectable, second-line agents
  - very difficult to treat, global public health threat, 5 documented cases in Canada from 1997-2008
  - suspect MDR TB if previous treatment, exposure to known MDR index case, or immigration from a high-risk area
- note: TB is a reportable disease to Public Health (please see Public Health Agency of Canada website for more information: www.phac-aspc.gc.ca/tbpc-latb/pubs/tb-canada-7/index-eng.php)
HIV and AIDS

Epidemiology

Canadian Situation (Public Health Agency of Canada, 2013)
- estimated 71,300 Canadians living with HIV infection at the end of 2011, 25% unaware of HIV-positive status
- 2,090 new infections were reported in 2013: MSM account for 49.3% of cases, IVDU 12.8%

Global Situation (WHO and UNAIDS Core Epidemiology Slides, July 2014)
- estimated 35 million people living with HIV/AIDS in 2013
- estimated 2.1 million newly infected in 2013
- estimated 1.5 million AIDS-related deaths in 2013

Definition and Pathophysiology

- HIV is a retrovirus that causes progressive immune system dysfunction which predisposes patients to various opportunistic infections and malignancies
- HIV virion includes an envelope (gp41 and gp120 glycoproteins), matrix (p17) and capsid (p24) enclosing 2 single-stranded copies of RNA + enzymes in its core
- virion glycoproteins bind CD4 and CXCR4/CCR5 on CD4+ T lymphocytes (T-helper cells) to fuse and enter the cells
- RNA converted to dsDNA by reverse transcriptase; dsDNA is integrated into host genome
- virus DNA transcribed and translated using host cell machinery, post-translational modifications include proteolytic activity of virally encoded protease enzymes
- newly produced virions bud out of host cell, incorporating host cell membrane; additional maturation steps are required before virion is considered infectious
- exact mechanisms of CD4 depletion incompletely characterized but likely include direct viral cytopathic effects, apoptosis, and increased cell turnover

Modes of Transmission

Table 20. Modes of Transmission by Site and Medium

<table>
<thead>
<tr>
<th>HIV Invasion Site</th>
<th>Sub-Location</th>
<th>Transmission Medium</th>
<th>Transmission Probability per Exposure Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female genital tract</td>
<td>Vagina, ectocervix, endocervix</td>
<td>Semen</td>
<td>1 in 200 to 1 in 2,000</td>
</tr>
<tr>
<td>Male genital tract</td>
<td>Inner foreskin, penile urethra</td>
<td>Cervicovaginal and rectal secretions and desquamations</td>
<td>1 in 700 to 1 in 3,000</td>
</tr>
<tr>
<td>Intestinal tract</td>
<td>Rectum</td>
<td>Semen</td>
<td>1 in 20 to 1 in 300</td>
</tr>
<tr>
<td>Intestinal tract</td>
<td>Upper GI tract</td>
<td>Semen</td>
<td>1 in 2,500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Maternal blood/genital secretions (intrapartum)</td>
<td>1 in 5 to 1 in 10</td>
</tr>
<tr>
<td>Placenta</td>
<td>Chorionic villi</td>
<td>Maternal blood (intrauterine)</td>
<td>1 in 10 to 1 in 20</td>
</tr>
<tr>
<td>Blood stream</td>
<td></td>
<td>Contaminated blood products</td>
<td>95 in 100</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sharp/needlestick injuries</td>
<td>1 in 150</td>
</tr>
</tbody>
</table>

Adapted with permission from Macmillan Publishers Ltd. Nat Rev Immunology 2008;8:447-457

NOTE: these estimates are for “all comers” i.e. they estimate transmission risk for anyone with HIV infection and do not take into account treatment status of the HIV+ person (in contrast to results of PARTNER study)
Natural History

Figure 10. Relationships between CD4 T-cell count, viral load, and anti-HIV antibodies

Acute (Infection) Retroviral Syndrome
- 40-90% experience an acute "flu-like" illness (may include fever, pharyngitis, lymphadenopathy, rash, arthralgias, myalgias, H/A, GI symptoms, oral ulcers, weight loss) 2-6 wk post-exposure lasting 10-15 d
- hematologic disturbances (lymphopenia, thrombocytopenia)
- 10-20% present with aseptic meningitis; HIV RNA and/or p24 may be detected in CSF
- associated with a high level of plasma viremia and therefore high risk of transmission

Asymptomatic (Latent) Stage
- during latent phase, HIV infects and replicates in CD4+ T lymphocytes (lymph nodes)
- normal CD4 count: 500-1,100 cells/mm³
- CD4 count drops 60-100 cells/mm³ per year
- by 10 yr post-infection, 50% have AIDS, 30% demonstrate milder symptoms, and <20% are asymptomatic if left untreated

AIDS Definition in Canada
- HIV-positive AND
- one or more of the clinical illnesses that characterize AIDS, including: opportunistic infections (e.g. PJP (previously PCP), esophageal candidiasis, CMV, MAC, TB, toxoplasmosis), malignancy (Kaposi’s sarcoma, invasive cervical cancer), wasting syndrome OR
- CD4 <200 (or <15%); this is largely historical since ART can reverse CD4 count decline

Table 21. Symptomatic Stage (CD4 count thresholds for classic clinical manifestations)

<table>
<thead>
<tr>
<th>CD4 Counts</th>
<th>Possible Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500 cells/mm³</td>
<td>Often asymptomatic. Constitutional symptoms: fever, night sweats, fatigue, weight loss Mucocutaneous lesions: seborrheic dermatitis, HSV, VZV (shingles), oral hairy leukoplakia (EBV), candidiasis (oral, esophageal, vaginal), Kaposi’s sarcoma (KS) Recurrent bacterial infections, especially pneumonia Pulmonary and extrapulmonary tuberculosis Lymphoma</td>
</tr>
<tr>
<td>&lt;200 cells/mm³</td>
<td>Pneumocystis jiroveci pneumonia (formerly PCP) KS Oral thrush Local and/or disseminated fungal infections: Cryptococcus neoformans, Coccidioides immitis, Histoplasma capsulatum</td>
</tr>
<tr>
<td>&lt;100 cells/mm³</td>
<td>Progressive multifocal leukoencephalopathy (PML) – JC virus CNS toxoplasmosis</td>
</tr>
<tr>
<td>&lt;50 cells/mm³</td>
<td>CMV infection: retinitis, colitis, cholangiopathy, CNS disease Mycobacterium avium complex (MAC) Bacillary angiomatosis (disseminated Bartonella) Primary central nervous system lymphoma (PCNSL)</td>
</tr>
</tbody>
</table>

Laboratory Diagnosis
- anti-HIV antibodies detectable after a median of 3 wk, virtually all by 3 mo (therefore 3 mo window period)
- initial screening test (3rd generation antibody test): enzyme linked immunosorbent assay (ELISA) detects serum antibody to HIV; sensitivity >99.5%
Management of the HIV-Positive Patient

• verify positive HIV test
• complete baseline history and physical exam, then follow-up every 3-6 mo
• laboratory evaluation
  • routine CD4 count to measure status of the immune system
  • also important indicator of effect of ART
  • baseline HIV resistance testing to guide ARV therapy
• HLA-B*5701 genetic test to screen for abacavir hypersensitivity
• baseline tuberculin skin test (PPD): induration greater than 5 mm is positive
• baseline serologies (hepatitis A, B, and C, syphilis, toxoplasma, CMV, VZV)
• routine biochemistry and hematology, CXR
• annual fasting lipid profile and fasting glucose (due to HAART side effects)
• education
  • regular follow-up on CD4 counts and viral loads (q3-6mo) as well as strict adherence to ART improves prognosis
  • prevention of further transmission through safer sex and clean needles for injection drug use
  • HIV superinfection (transmission of different HIV strains from another HIV+ person) does rarely occur so barrier protection during sex is still recommended
• discuss importance of disclosing HIV status to partners including risk of criminal prosecution of non-disclosure in jurisdictions where applicable
• connect to relevant community groups and resources
• health care maintenance
  • assessment of psychosocial concerns and referral to psychiatry or social work if appropriate
  • vaccines: influenza annually, 23-valent pneumococcal every 5 yr, HBV (if not immune), HAV (if seronegative)
  • annual screening (PAP smear, STIs)
• management of comorbid conditions and provision of general primary care

Table 22. Prophylaxis Against Opportunistic Infections in HIV-infected Patients

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Indication for Prophylaxis</th>
<th>Prophylactic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pneumocystis jiroveci</td>
<td>CD4 count &lt;200 cells/mm³ or history of oral candidiasis</td>
<td>TMP-SMX 1 SS or DS OD</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>IgG antibody to Toxoplasma and CD4 count &lt; 100 cells/mm³</td>
<td>As per prophylaxis for pneumocystis</td>
</tr>
<tr>
<td>Mycobacterium tuberculosis</td>
<td>PPD reaction &gt;5 mm or contact with case of active TB</td>
<td>INH + pyridoxine daily x 9 mo</td>
</tr>
<tr>
<td>Mycobacterium avium complex</td>
<td>CD4 count &lt;50 cells/mm³</td>
<td>Azithromycin 1,200 mg q1wk</td>
</tr>
</tbody>
</table>

SS = single strength; DS = double strength

Anti-Retroviral Treatment

Overall Treatment Principles
• recommended that all HIV+ patients initiate HAART to prevent disease progression and transmission; strength of evidence supporting this recommendation changes depending on CD4 count and sexual practices (AI evidence that CD4 350 should be on HAART)
• patients starting HAART should be committed to treatment and understand the importance of adherence; poor compliance can lead to viral resistance; may defer treatment on the basis of clinical and psychosocial factors on case by case basis
• initiate ART if opportunistic infection/malignancy, pregnancy, HIV-associated nephropathy, HIV-associated thrombocytopenia, need for hepatitis B therapy in HBV co-infected patients
• consider starting treatment early if HCV co-infection, high HIV viral load, comorbid conditions (e.g. cardiovascular disease)
• consider results of baseline resistance testing and complete ART history before (re-)initiating HAART
• goal: keep viral load below limit of detection i.e. <40 copies/mL (undetectable); viral load should decrease 10-fold within 4-8 wk, be undetectable by 6 mo, and restore immunologic function
• strong evidence against intermittent HAART or ‘drug holidays’
• ART leads to 96% reduction in risk of transmitting HIV to sexual partners

Viral load: rate of progression
• CD4 count: progress and stage of disease

HIV Status
• 1° and 2° prophylaxis may be discontinued if CD4 count is above threshold for ≥6 mo while on ART

HLA-B*5701 Testing
Abacavir hypersensitivity reactions usually only occur in individuals carrying this HLA allele (~5-7% of Caucasians, lower prevalence in other ethnic groups). Routine screening for HLA-B*5701 at baseline and definitely prior to abacavir use

Reasons for Deterioration of a Patient with HIV/AIDS
• Opportunistic infections
• Neoplasms
• Medication-related toxicities
• Co-infections (e.g. HBV, HCV, STIs)
• Non-AIDS-related comorbidities (e.g. cardiovascular, renal, hepatic, neurocognitive, bone disease)
HAART Recommendations for Treatment of Naïve Patients

- 2 NRTIs + 1 INSTI/NNRTI/PI (boosted with ritonavir or cobicistat)

Treatment Failure

- defined clinically (HIV progression), immunologically (failure to increase CD4 count by 25-50 over first yr of treatment or CD4 decrease >100 over 1 yr), or virologically (failure to achieve viral load <40 copies/mL after 6 mo)
- ensure that viral load >40 is not just a transient viremia or 'blip'; confirm medication adherence, assess drug interactions, perform resistance testing

Table 23. Anti-Retroviral Drugs

<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside reverse transcriptase inhibitors (NRTIs)</td>
<td>zidovudine (AZT)</td>
<td>Incorporated into the growing viral DNA chain, thereby competitively inhibiting reverse transcriptase and terminating viral DNA growth</td>
<td>Lactic acidosis</td>
</tr>
<tr>
<td></td>
<td>lamivudine (3TC)</td>
<td></td>
<td>Lipodystrophy</td>
</tr>
<tr>
<td></td>
<td>stavudine (d4T)</td>
<td></td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td>didanosine (ddI)</td>
<td></td>
<td>N/V/diarrhea</td>
</tr>
<tr>
<td></td>
<td>abacavir (ABC)</td>
<td></td>
<td>Bone marrow suppression (AZT)</td>
</tr>
<tr>
<td></td>
<td>emtricitabine (FTC)</td>
<td></td>
<td>Peripheral neuropathy (ddI, d4T)</td>
</tr>
<tr>
<td></td>
<td>tenofovir disoproxil fumarate (TDF)</td>
<td></td>
<td>Drug-induced hypersensitivity (ABC)</td>
</tr>
<tr>
<td>Combination Tablets:</td>
<td>AZT/3TC (Combivir®)</td>
<td></td>
<td>Pancreatitis (ddI/d4T)</td>
</tr>
<tr>
<td></td>
<td>AZT/3TC/ABC (Trizivir®)</td>
<td></td>
<td>Myopathy (AZT)</td>
</tr>
<tr>
<td></td>
<td>ABC/3TC (Kivexa®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>TDF/FTC (Truvada®)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</td>
<td>efavirenz (EFZ)</td>
<td>Non-competitively inhibit function of reverse transcriptase, thereby preventing viral RNA replication</td>
<td>Rash, Stevens-Johnson syndrome</td>
</tr>
<tr>
<td></td>
<td>nevirapine (NVP)</td>
<td></td>
<td>CNS: dizziness, insomnia, somnolence, abnormal dreams (efavirenz)</td>
</tr>
<tr>
<td></td>
<td>delavirdine (DLV)</td>
<td></td>
<td>Hepatotoxicity (nevirapine – avoid in females with CD4 &gt; 250, men with CD4 &gt; 400)</td>
</tr>
<tr>
<td></td>
<td>etravirine (ETR)</td>
<td></td>
<td>CYP3A4 interactions</td>
</tr>
<tr>
<td></td>
<td>rilpivirine (RPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitors (PIs)*</td>
<td>ritonavir (RTV)</td>
<td>Prevent maturation of infectious virions by inhibiting the cleavage of polypeptides</td>
<td>Lipodystrophy, metabolic syndrome</td>
</tr>
<tr>
<td></td>
<td>saquinavir (SQV)</td>
<td></td>
<td>N/V/diarrhea</td>
</tr>
<tr>
<td></td>
<td>amprenavir (APV)</td>
<td></td>
<td>Nephrolithiasis (indinavir)</td>
</tr>
<tr>
<td></td>
<td>nelfinavir (NFV)</td>
<td></td>
<td>Rash (APV)</td>
</tr>
<tr>
<td></td>
<td>indinavir (IDV)</td>
<td></td>
<td>Hyperbilirubinemia (atazanavir, indinavir)</td>
</tr>
<tr>
<td></td>
<td>atazanavir (ATV)</td>
<td></td>
<td>CYP3A4 interactions</td>
</tr>
<tr>
<td></td>
<td>fosamprenavir (FPV)</td>
<td></td>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>lopinavir (LPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>tipranavir (TPV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>darunavir (DRV)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fusion inhibitor</td>
<td>enfuvirtide (T-20)</td>
<td>Inhibit viral fusion with T-cells by inhibiting gp41, preventing cell infection</td>
<td>Injection site reactions, rash, infection, diarrhea, nausea, fatigue</td>
</tr>
<tr>
<td>CCR5 antagonist</td>
<td>maraviroc</td>
<td>Inhibit viral entry by blocking host CCR5 co-receptor</td>
<td>Fever, cough, dizziness</td>
</tr>
<tr>
<td>Integrase strand transfer inhibitors (INSTIs)</td>
<td>raltegravir</td>
<td>Inhibits integration of HIV DNA into the human genome thus preventing HIV replication</td>
<td></td>
</tr>
<tr>
<td></td>
<td>elvitegravir</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>dolutegravir</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Standard of care is to pharmacologically boost most PIs with ritonavir to increase concentrations

Single Tablet ART Regimens

- reduces pill burden and increases adherence
- generally better tolerated

Table 24. Single Tablet HAART Regimens

<table>
<thead>
<tr>
<th>Name</th>
<th>Contents</th>
<th>Common Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atripla®</td>
<td>efavirenz/tenofovir/emtricitabine</td>
<td>psychiatric events, vivid dreams</td>
</tr>
<tr>
<td>Complera®</td>
<td>ritonavir/emtricitabine/tenofovir</td>
<td>good side effect profile</td>
</tr>
<tr>
<td>Striroid®</td>
<td>elvitegravir/cobicistat/emtricitabine/tenofovir</td>
<td>good side effect profile</td>
</tr>
<tr>
<td>Triumeq®</td>
<td>Dolutegravir/abacavir/lamivudine</td>
<td>good side effect profile; use only in HIVAB*5701 negative patients</td>
</tr>
</tbody>
</table>
Prevention of HIV Infection

- education, including harm-reduction
  - safer sexual practices: condoms for vaginal and anal sex, barriers for oral sex
  - harm reduction for injection drug users: avoid sharing needles
- treatment of HIV+ women with HAART during the 2nd and 3rd trimester of pregnancy and AZT during delivery followed by treatment of the infant for 6 wk (decreases maternal-fetal transmission from 25% to <3%)
- universal blood and body precautions for health care workers
  - post-exposure prophylaxis (PEP) after occupational (e.g. needle-stick injury) and non-occupational (e.g. consensual sex, sexual assault) exposure to HIV: 2- or 3-drug regimen initiated immediately (<72 h) after exposure and continuing for 4 wk
- recent data has demonstrated efficacy of pre-exposure prophylaxis (oral PrEP or topical microbicides) in preventing HIV although additional data needed
- ART associated with 96% reduction in risk of transmitting HIV to sexual partners
- screening of blood and organ donation
**Types of Testing**

1. **Nominal/Name-Based HIV Testing**
   - person ordering the test knows the identity of the person being tested for HIV
   - HIV test is ordered using the name of the person being tested
   - person ordering the test is legally obligated to notify Public Health officials if test results are positive for HIV
   - test result is recorded in the health care record of the person being tested

2. **Non-Nominal/Non-Identifying HIV Testing**
   - similar to nominal/name-based testing on all points except:
     - HIV test is ordered using a code or the initials of the person being tested

3. **Anonymous Testing**
   - available at specialized clinics
   - person ordering the HIV test does not know the identity of the person being tested
   - HIV test is carried out using a unique non-identifying code that only the person being tested for HIV knows
   - test results are not recorded on the health care record of the person being tested
   - patient identification and notification of Public Health required to gain access to ART

**HIV Pre- and Post-Test Counselling**

- a diagnosis of HIV can be overwhelming and is often associated with stigma and discrimination
- consider pre- and post-test counselling, regardless of the results
- goals include: assessing risk, making informed decision to be tested, education to protect themselves and others from virus exposure, where to go for more information and support
- HIV+ patients should be connected with local support services

**Fungal Infections**

**Skin and Subcutaneous Infections**

**Superficial Fungal Infections**
- see **Dermatology, D27**

**Dermatophytes**
- see **Dermatology, D27**

**Subcutaneous Fungal Infection**

**Pathophysiology**
- fungi that naturally reside in soil and enter skin via traumatic break
  - *Sporothrix schenckii*: most commonly affects gardeners injured by a rose thorn or splinter
    - causes subcutaneous nodule at point of entry
    - fungi may migrate up lymphatic vessels creating nodules along the way – “nodular lymphangitis”

**Treatment**
- oral azole (e.g. itraconazole)
- IV amphotericin B for severe or disseminated infection

**Endemic Mycoses**

**Basics**
- three major endemic mycoses in North America
  - histoplasmosis
  - blastomycosis
  - coccidioidomycosis

Histoplasmosis is commonly associated with exposure to chicken coops, bird roosts, and bat caves
• thermally dimorphic organisms: mold in cold temperature (e.g. soil) and yeast at higher temperature (e.g. tissue)
• infection occurs through inhalation of spores (soil, bird droppings, vegetation) or inoculation injury
• all can cause pneumonia and may disseminate hematogenously
• may reactivate or disseminate during immunocompromised states

Treatment
• common to all endemic mycoses
  • oral azole (e.g. itraconazole for mild-moderate local infection)
  • IV amphotericin B for systemic infection

Table 25. Endemic Mycoses

<table>
<thead>
<tr>
<th>Disease</th>
<th>Endemic Region</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histoplasma capsulatum</td>
<td>Ohio and Mississippi River valleys in central USA, Ontario, Quebec; widespread</td>
<td>Asymptomatic (in most people) Primary pulmonary • Fever, cough, chest pain, H/A, myalgia, anorexia • CXR (acute): pulmonary infiltrates ± hilar lymphadenopathy • CXR (chronic): pulmonary infiltrates, cavitary disease Disseminated (rare) • Occurs primarily in immunocompromised patients • Spread to bone marrow (pancytopenia), GI tract (ulcers), lymph nodes (lymphadenitis), skin, liver, adrenals, CNS</td>
<td>Fungal culture, fungal stain Antigen detection (urine and serum) Serology</td>
</tr>
<tr>
<td>Blastomyces dermatitidis</td>
<td>States east of Mississippi River, Northern Ontario and along the Great Lakes</td>
<td>May be asymptomatic Primary: acute or chronic pneumonia • Fever, cough, chest pain, chills, night sweats, weight loss • CXR (acute): lobar or segmental pneumonia • CXR (chronic): lobar infiltrates, fibronodular interstitial disease Disseminated • Spread to skin (verrucous lesions that mimic skin cancer, ulcers, subcutaneous nodules), bones (osteomyelitis, osteolytic lesions), GU tract (prostatitis, epididymitis)</td>
<td>Sputum smear and culture Direct examination of clinical specimens for characteristic broad-based budding yeast (sputum, tissue, purulent material)</td>
</tr>
<tr>
<td>Coccidioides immitis</td>
<td>Deserts in southwest USA, northwest Mexico</td>
<td>Primary • “Valley fever”: subacute fever, chills, cough, chest pain, sore throat, fatigue that lasts for weeks to months • Can develop hypersensitivity with arthralgias, erythema nodosum Disseminated • Rare spread to skin (ulcers), joints (synovitis), bones (lytic lesions), meninges (meningocephalitis) • Common opportunistic infection in patients with HIV</td>
<td>Sputum culture Direct examination of clinical specimens for characteristic yeast (sputum, tissue, purulent material)</td>
</tr>
</tbody>
</table>

Opportunistic Fungi

Pneumocystis jiroveci (formerly P. carinii)
Pneumonia: PJP or PCP

Microbiology
• unicellular fungi
• previously classified as a protozoa

Transmission
• rarely person-to-person transmission
• most disease is due to reactivation of latent infection acquired by the respiratory route or reinfestation by a different genotype
  • causes clinical disease in immunocompromised patients (steroid use, HIV)
  • 80% lifetime risk without prophylaxis (TMP/SMX) in HIV patients with CD4 count <200 cells/mm³

Clinical Features
• symptoms of pneumonia: fever, nonproductive cough, progressive dyspnea
• classic CXR

Investigations
• demonstration of organism in induced sputum, bronchoalveolar lavage, or endotracheal aspirate (if intubated)
Treatment and Prevention
• oxygen to keep SaO₂ >90%
• antimicrobial options
  ▪ TMP/SMX (PO or IV)
  ▪ dapsone and TMP
  ▪ clindamycin and primaquine
  ▪ pentamidine (IV)
  ▪ atovaquone
• corticosteroids used as adjuvant therapy in those with severe hypoxia (pO₂ <70 mmHg or A-a gradient O₂ >35 mmHg)
• prophylactic TMP/SMX for those at high risk of infection (HIV patients when CD4 <200 cells/mm³ or non-HIV immunocompromised patients under specific conditions)

**Cryptococcus spp.**

Microbiology
• encapsulated yeast found worldwide
• 2 human pathogenic species: *C. gattii*, *C. neoformans*

Transmission
• inhalation of airborne yeast from soil contaminated with pigeon droppings (*C. neoformans*) or certain tree species such as Eucalyptus or Douglas fir (*C. gattii*) → may cause local infection in lung → asymptomatic or pneumonia
• may also spread hematogenously to the CNS, skin, bones, and other organs
• *C. neoformans* tends to affect immunocompromised hosts
• *C. gattii* tends to affect immunocompetent hosts

Clinical Features
• pulmonary
  ▪ usually asymptomatic or self-limited pneumonia
  ▪ only 2% of HIV+ patients present with pulmonary symptoms including productive cough, chest tightness, and fever
• disseminated
  ▪ frequently disseminates in HIV+ population
  ▪ CNS: meningitis (leading cause of meningitis in patients with HIV)
  ▪ skin: umbilicated papules that resemble large lesions of *Molluscum contagiosum*

Investigations
• serum cryptococcal antigen
• CSF for meningitis: India-ink stain, cryptococcal antigen test, culture to confirm

Treatment
• in patients with HIV who have cryptococcal meningitis or severe pulmonary disease:
  ▪ amphotericin B (+ flucytosine) is used in the first 2 wk for induction therapy; limited duration due to side effects
  ▪ switch to fluconazole for at least 8 wk as consolidation therapy, then continue at lower dose for prolonged maintenance

**Candida albicans**

Microbiology
• yeast forms with pseudohyphae germ tube formation at 37°C

Transmission
• normal flora of skin, mouth, vagina, and GI tract
• risk factors for overgrowth:
  ▪ immunocompromised state (DM, corticosteroids)
  ▪ ICU patients (broad-spectrum antibiotic use, central venous catheters, TPN)
  ▪ obesity → maceration and moisture in intertriginous areas, pannus, under breasts

Clinical Features
• mucocutaneous
  ▪ oral thrush, esophagitis (chest pain, odynophagia), vulvovaginitis (see Gynecology, GY27), balanitis, cutaneous (diaper rash, skin folds, folliculitis), chronic mucocutaneous
  ▪ small satellite lesions beyond the margin of the rash
• invasive
  ▪ candidemia, endophthalmitis, endocarditis, UTI (upper tract), hepatosplenic disease
Treatment
- thrush: nystatin suspension or pastilles for mild disease, fluconazole for severe disease
- vulvovaginal candidiasis: topical agents (imidazole or nystatin), oral fluconazole for recurrent disease
- cutaneous infection: topical imidazole
- opportunistic infections in HIV, other systemic infections: fluconazole or echinocandin
- chronic mucocutaneous: azoles

Aspergillus spp.

Microbiology
- branching septate hyphae
- common species causing disease include A. fumigatus, A. fla

Transmission
- ubiquitous in the air and the environment
- Aspergillus produces a toxin called aflatoxin that contaminates nuts, grains, and rice

Clinical Features
- allergic bronchopulmonary aspergillosis (ABPA)
- IgE-mediated asthma-type reaction with dyspnea, high fever, and transient pulmonary infiltrates
- occurs more frequently in patients with asthma and allergies
- aspergilloma (fungus ball)
- ball of hyphae in a preexisting lung cavity
- symptoms range from asymptomatic to massive hemoptyis
- CXR: round opacity surrounded by a thin lucent rim of air, often in upper lobes (“air crescent” sign)
- invasive aspergillosis
- associated with prolonged and persistent neutropenia or transplantation
- pneumonia – most common
- may disseminate to other organs: brain, skin
- severe symptoms with fever, cough, dyspnea, cavitation; fatal if not treated early and aggressively
- CXR: local or diffuse infiltrates ± pulmonary infarction, pulmonary nodules with surrounding ground glass (“halo” sign)
- mycotoxicosis
- aflatoxin produced by A. flavus (nuts, grains, rice)
- results in liver hemorrhage, necrosis, and hepatocellular carcinoma formation

Treatment Options
- for invasive aspergillosis: voriconazole or amphotericin B
- surgical resection for aspergilloma
- corticosteroids ± itraconazole for ABPA

Parasitic Infections

Protozoa – Intestinal/Genitourinal Infections

Entamoeba histolytica (Amoebas)

Transmission
- reservoir: infected humans
- cysts by fecal-oral and food/waterborne transmission in areas of poor sanitation
- seen in immigrants, travellers, institutionalized individuals, Aboriginal Canadians, MSM

Clinical Features
1. asymptomatic carriers
2. amoebic dysentery
   - abdominal pain, cramping, colitis, dysentery, low grade fever with bloody diarrhea
   secondary to local tissue destruction and ulceration of large intestine
3. amoebic abscesses
   - most common in liver (hematologic spread); presents with RUQ pain, weight loss, fever, hepatomegaly
   - can also occur in lungs and brain

Figure 12. Entamoeba life cycle
Investigations
- serology, fecal/serum antigen testing, stool exam (for cysts and trophozoites), colon biopsy
- *E. histolytica* indistinguishable microscopically from the non-pathogen *E. dispar* (distinguish by specific stool antigen detection)

Treatment and Prevention
- metronidazole
- for invasive disease or cyst elimination: follow with iodoquinol or paromomycin
- aspiration of hepatic abscess if risk of cyst rupture, poor response to medical therapy, or diagnostic uncertainty
- asymptomatic cyst shedding: iodoquinol or paromomycin alone
- good personal hygiene, purification of water supply by boiling, filtration (not chlorination)

### Giardia lamblia

**Transmission**
- reservoir: infected humans and other mammals
- food/waterborne (especially in the Rockies) and fecal-oral transmission of infectious cysts
- risk factors: travel, camping, institutions, day care centres, MSM

**Clinical Features**
- giardiasis (“beaver fever”)
  - symptoms vary from asymptomatic to self-limited mild watery diarrhea to malabsorption syndrome (chronic giardiasis where the parasite coats the small intestine and thus prevents fat absorption)
  - nausea, malaise, abdominal cramps, bloating, flatulence, fatigue, weight loss, steatorrhea
  - no hematochezia (no invasion into intestinal wall), no mucous in stool

**Investigations**
- multiple stool samples (daily x 3 d) for microscopy, stool antigen used occasionally
- occasionally small bowel aspirate or biopsy

**Treatment and Prevention**
- metronidazole; nitazoxanide if symptomatic
- good personal hygiene and sanitation, water purification (iodine better than chlorination), outbreak investigation

### Trichomonas vaginalis

**Transmission**
- sexual contact

**Clinical Features**
- often asymptomatic (10-50%), especially males (occasionally urethritis, prostatitis)
- *trichomonas vaginalis* (see Gynecology, GY27)
  - vaginal discharge (profuse, malodourous, yellow-green or grey, frothy), pruritus, dysuria, dyspareunia

**Investigations**
- wet mount (motile parasites), antigen detection, culture
- urine PCR to detect in males

**Treatment**
- metronidazole for patient and partner(s)

### Cryptosporidium spp.

**Transmission**
- reservoir: infected humans and a wide variety of young animals
- fecal-oral transmission by ingestion of cysts; waterborne
- risk factors: summer and fall, young children (day care), MSM, contact with farm animals, immunodeficiency

**Clinical Features**
- range from self-limited watery diarrhea (immunocompetent) to chronic, severe, non-bloody diarrhea with N/V, abdominal pain, and anorexia resulting in weight loss and death (immunocompromised)
Investigations
- modified acid-fast stain of stool specimen, microscopic identification of oocysts in stool or tissue, stool antigen detection by direct fluorescent antibody

Treatment and Prevention
- supportive care
- in HIV, try HAART to restore immunity; if fails, try nitazoxanide
- good personal hygiene, water filtration

Blood and Tissue Infections

Plasmodium spp. (Malaria)

Microbiology
- species include: P. falciparum (most common and most lethal), P. vivax, P. ovale, P. malariae, P. knowlesi (new species isolated from primates in Malaysia, potentially fatal)
- complex life cycle: human host for asexual reproduction and mosquito for sexual reproduction
- sporozoites from mosquitoes infect human liver cells, where they multiply and are released as merozoites; merozoites infect RBCs and cause disease
- P. ovale and P. vivax can produce dormant hypnozoites in the liver that may cause relapsing malarial attacks by reactivating (entering the erythrocytic cycle) after many months

Transmission
- reservoir: infected human
- transmission by the night-biting female Anopheles mosquito, vertical transmission, and blood transfusion
- occurs in tropical/subtropical regions (sub-Saharan Africa, Oceania, South Asia, Central America, Southeast Asia, South America)

Clinical Features
- flu-like prodrome
- paroxysms of high spiking fever and shaking chills (due to synchronous systemic lysis of RBCs) (lasts several hours)
  - P. vivax and P. ovale: chills and fever x48h but can be variable
  - P. malariae: chills and fever x72h but can be variable
  - P. falciparum: less predictable fever interval, can be highly variable (>90% ill within 30 d)
- abdominal pain, diarrhea, myalgia, H/A, and cough
- hepatosplenomegaly and thrombocytopenia without leukocytosis

Complications
- P. falciparum: CNS involvement (cerebral malaria = seizures and coma), severe anemia, acute kidney injury, ARDS, primarily responsible for fatal disease
- P. knowlesi, and rarely P. vivax, can be fatal

Investigations
- microscopy: blood smear q12-24h (x3) to rule out infection
  - thick smear (Giemsa stain) for presence of organisms
  - thin smear (Giemsa stain) for species identification and quantification of parasites
  - rapid antigen detection tests

Treatment and Prevention
- P. vivax, P. ovale: chloroquine (and primaquine to eradicate liver forms)
- P. vivax, chloroquine resistant: atovaquone/proguanil + primaquine or quinine and doxycycline + primaquine
- P. malariae, P. knowlesi: chloroquine
- P. falciparum: most areas of the world show chloroquine resistance – check local resistance patterns
  - artemisinin combination therapy (e.g. artesunate + doxycycline or clindamycin or atovaquone/proguanil)
  - atovaquone/proguanil combination (Malarone®)
  - quinine + doxycycline or clindamycin
  - mefloquine and artemisinin resistance increasing in southeast Asia (check local resistance)
- prevention with antimalarial prophylaxis, covering exposed skin, net insect repellent

Malaria is the most common fatal infectious disease worldwide

Figure 13. Life cycle of Plasmodium spp.

Drugs for Preventing Malaria in Travellers
Cochrane Database Syst Rev 2008;CD006491
Study: Cochrane Systematic Review. 8 RCTs.
Population: 4,240 non-immune adults and children traveling to regions with P. falciparum resistance to chloroquine.
Intervention: Atovaquone-proguanil, doxycycline, mefloquine, chloroquine-proguanil, or primaquine used for malaria prophylaxis.
Outcome: Efficacy, safety, and tolerability.
Results: Atovaquone-proguanil and doxycycline had similar adverse events. Atovaquone-proguanil had fewer overall (RR 0.72), GI (RR 0.54), and neuropsychiatric events (RR 0.48) than mefloquine. Dapsone also had fewer neuropsychiatric events than mefloquine (RR 0.84).
Conclusion: Atovaquone-proguanil or doxycycline as prophylaxis against malaria is best tolerated in terms of adverse effects and mefloquine is associated with adverse neuropsychiatric outcomes.
**Trypanosoma cruzi**

**Transmission**
- found in Mexico, South America, and Central America
- transmission by Reduviid insect vector ("Kissing Bug"), which defecates on skin and trypanomastigotes in the stool are rubbed into bite site by host
- also transmitted via placental transfer, organ donation, blood transfusion, and ingestion of contaminated food containing Reduviid insects (especially cane juice)

**Clinical Features**
- American trypanosomiasis (Chagas disease)
  - acute: usually asymptomatic, local swelling at site of inoculation ("Romana’s sign"; usually around one eye) with variable fever, lymphadenopathy, cardiomegaly, and hepatosplenomegaly
  - chronic indeterminate phase: asymptomatic but increasing levels of antibody in blood; most infected persons (60-70%) remain in this phase, and do not go on to manifest a determine form of Chagas disease
  - chronic determinate: leads to chronic dilated cardiomyopathy, esophagomegaly, and megacolon 10-25 yr after acute infection in 30-40% of infected individuals

**Investigations**
- wet prep and Giemsa stain of thick and thin blood smear, serology, PCR

**Treatment and Prevention**
- acute: nifurtimox or benznidazole
- indeterminate: increasing trend to treat as acute infection
- chronic determinate: symptomatic therapy, surgery as necessary including heart transplant, esophagectomy, and colectomy; there may be a benefit to antiparasitic treatment
- insect control, bed nets

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**Toxoplasma gondii**

**Transmission**
- acquired through exposure to cat feces (oocysts), ingestion of undercooked meat (tissue cysts), vertical transmission, organ transplantation, gardening without gloves (cat oocyst exposure), whole blood transfusions

**Clinical Features**
- congenital
  - result of acute primary infection of mother during pregnancy (TORCH infection – see Obstetrics, OB31)
  - stillbirth (rare), chorioretinitis, blindness, seizures, severe developmental delay, microcephaly
  - initially asymptomatic infant may develop reactivation of chorioretinitis as adolescent or adult → blurred vision, scotoma, ocular pain, photophobia, epiphora, hearing loss, developmental delay
- acquired
  - usually asymptomatic or mononucleosis-like syndrome in immunocompetent patient
  - infection remains latent for life unless reactivation due to immunosuppression
- immunocompromised (most commonly AIDS with CD4 <200)
  - encephalitis with focal CNS lesions seen as single or multiple ring-enhancing masses on CT (H/A and focal neurological signs)
  - lymph node, liver, and spleen enlargement and pneumonitis
  - chorioretinitis

**Investigations**
- serology, CSF Wright-Giemsa stain, antigen or DNA detection (PCR); pathology provides definitive diagnosis
- immunocompromised patients: consider CT scan (ring-enhancing lesion in cortex or deep nuclei) and ophthalmologic examination
- negative serology in many AIDS patients (false negative due to decreased lymphocyte population)

**Treatment and Prevention**
- no treatment if: immunocompetent, not pregnant, no severe organ damage
- pregnancy: spiramycin to prevent transplacental transmission or pyrimethamine + sulfadiazine (add folic acid), avoid undercooked meat and refrain from emptying cat litter boxes
- HIV: pyrimethamine + sulfadiazine (see Prophylaxis, ID31)
- eye disease, meningitis: corticosteroids
- proper hand hygiene, cook meat thoroughly to proper temperature

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**1/3 of Ontario’s population is infected with Toxoplasma gondii**

**Figure 14. Life cycle of Toxoplasma gondii**

**Classic Triad of Congenital Toxoplasmosis**
- Chorioretinitis
- Hydrocephalus
- Intracranial calcifications
# Helminths

## Roundworms – Nematodes

Table 26. Nematodes (Roundworms)

<table>
<thead>
<tr>
<th>Nematode</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Ascaris lumbricoides</em></td>
<td>Tropics</td>
<td>Human feces, ingestion of contaminated food or water containing eggs</td>
<td>Abdominal pain and intestinal obstruction from high worm burden</td>
<td>Mebendazole OR albendazole OR pyrantel pamoate</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Cough, dyspnea, pulmonary infiltrates from larval migration through lungs (Löffler’s syndrome)</td>
<td></td>
</tr>
<tr>
<td><em>Trichuris trichiura</em></td>
<td>Tropics</td>
<td>Ingestion of eggs in soil</td>
<td>Diarrhea (± mucous, blood), abdominal pain, rectal prolapse, stunted growth</td>
<td>Mebendazole OR albendazole</td>
</tr>
<tr>
<td><em>Onchocerca volvulus</em></td>
<td>Africa, Latin America</td>
<td>Blackfly bite</td>
<td>River blindness (onchocerciasis), dermatitis</td>
<td>Ivermectin + doxycycline</td>
</tr>
<tr>
<td><em>Wuchereria bancrofti</em></td>
<td>Tropics</td>
<td>Mosquito bite</td>
<td>Damage to lymphatics resulting in lymphadenopathy, lymphedema, and elephantiasis</td>
<td>Diethylcarbamazine + doxycycline</td>
</tr>
<tr>
<td><em>Loa Loa</em></td>
<td>Central Africa</td>
<td>Deer fly bite</td>
<td>Subcutaneous migration of worm, hyperresponsiveness in travellers</td>
<td>Diethylcarbamazine</td>
</tr>
<tr>
<td><em>Enterobius vermicularis</em></td>
<td>Worldwide</td>
<td>Human host: fecal-oral self-inoculation and fomite person-to-person transfer</td>
<td>Asymptomatic carriers or severe nocturnal perianal itching (pruritus ani) Occasional vaginitis, ectopic migration to appendix or other pelvic organs Abdominal pain, N/V with high worm burden</td>
<td>Sticky tape test: eggs adhere to tape applied to perianal skin (need 5-7 tests to rule out) Examination of perianal skin at night may reveal adult worms Usually no eosinophilia as no tissue invasion Mebendazole, albendazole; pyrantel in pregnancy Change underwear, bathe in morning, pajamas to bed, wash hands, trim fingernails Treat all family members simultaneously Reinfection common</td>
</tr>
<tr>
<td><em>Strongyloides stercoralis</em></td>
<td>Subtropical, tropical, and temperate (including southern US)</td>
<td>Fecal contamination of soil: transmission via unbroken skin, walking barefoot Autoinfection: penetration of larvae through GI mucosa or perianal skin Adult worms live in mucosa of small intestine</td>
<td>One of few worms able to multiply in human host Mostly asymptomatic infection or can have pruritic dermatitis at site of larval penetration Transient pulmonary symptoms during pulmonary migration of larvae (eosinophilic pneumonitis = Löffler’s syndrome) Abdominal pain, diarrhea, pruritis ani, larva currens (itchy rash) Hyperinfection: occasional fatal cases caused by massive auto-infection in immunocompromised host; immunosuppressive therapy, including high-dose corticosteroids, is the most common risk factor for disseminated infection</td>
<td>Ivermectin, 200 µg/kg/d PO x 2 doses (albendazole 400 mg PO bid x 7 d, less effective)</td>
</tr>
</tbody>
</table>

**Figure 15. Life cycle of Enterobius**

1. Embryonated eggs ingested by humans
2. Larvae hatch in small intestine
3. Females migrate out anus at night

**Figure 16. Life cycle of Strongyloides**

1. Step on stool containing larvae
2. Larvae migrate to lungs via bloodstream
3. Larvae crawl up trachea and down to GI tract (cough/swallow)
4. Adult worms in intestine
5. Eggs produced in bowel
6. Larva
7. Bowel movement containing larvae
### Flatworms

#### Cestodes/Trematodes

**Table 27. Cestodes/Trematodes (Flatworms)**

<table>
<thead>
<tr>
<th>CESTODES</th>
<th>Epidemiology</th>
<th>Transmission</th>
<th>Medical Importance</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Taenia solium</em></td>
<td>Developing countries</td>
<td>Undercooked pork (larvae), human feces (eggs)</td>
<td>Taeniasis: mild abdominal symptoms Cysticercosis: mass lesions in CNS, eyes, skin, seizures</td>
<td>Corticosteroids + albendazole for cysticercosis Antiepileptics if seizures Praziquantel for adult tapeworm in gut (taeniasis)</td>
</tr>
<tr>
<td><em>Taenia saginata</em></td>
<td>Developing countries</td>
<td>Undercooked beef (larvae)</td>
<td>Mild GI symptoms</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Diphyllobothrium latum</em></td>
<td>Europe, North America, Asia</td>
<td>Raw fish</td>
<td>B12 deficiency leading to macrocytic anemia and posterior column deficits</td>
<td>Praziquantel</td>
</tr>
<tr>
<td><em>Echinococcus granulosus</em></td>
<td>Rural areas Sheep-raising countries</td>
<td>Dog feces (eggs)</td>
<td>Liver/lung cysts (enlarge between 1-20 yr; may cause mass effect or rupture) Risk of anaphylaxis if cystic fluid released during surgical evacuation</td>
<td>Albendazole ± praziquantel alone Surgery + perioperative albendazole Percutaneous aspiration + perioperative albendazole</td>
</tr>
</tbody>
</table>

**TREMATODES**

<table>
<thead>
<tr>
<th>Trematodes/Flukes</th>
<th>Species</th>
<th>Transmission</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Clonorchis sinensis</em></td>
<td>Japan, Taiwan, China, SE Asia Raw fish</td>
<td>Exists in bile ducts, causes inflammation and sometimes cholangiocarcinoma</td>
<td>most asymptomatic; symptoms seen in travellers (nonimmune)</td>
</tr>
<tr>
<td><em>Schistosoma spp.</em></td>
<td>Africa, SE Asia, focal in Western Hemisphere Fresh water exposure</td>
<td>Chronic sequelae secondary to long-term infection (e.g. chronic liver disease, SCC of the bladder)</td>
<td></td>
</tr>
</tbody>
</table>

#### Schistosoma spp.

**Species**
- *S. mansoni*, *S. hematobium*, *S. japonicum*

**Transmission**
- larvae ( cercariae), released from snails, penetrate unbroken skin in infested fresh water
- adult worms live in terminal venules of bladder/bowel passing eggs into urine/stool
- eggs must reach fresh water to hatch; schistosomes cannot multiply in or pass between humans
  - more common in individuals from sub-Saharan Africa, South America, Asia, Caribbean, Eastern Mediterranean/North Africa

**Clinical Features**
- most asymptomatic; symptoms seen in travellers (nonimmune)
- swimmer’s itch: pruritic skin rash at site of penetration (cercarial dermatitis)
- acute schistosomiasis (Katayama fever): hypersensitivity to migrating parasites (4-8 wk after infection)
  - fever, hives, H/A, weight loss, cough, abdominal pain, chronic diarrhea, high-grade eosinophilia

**Complications of Chronic Infection**
- *S. mansoni*, *S. japonicum*
  - worms in mesenteric vein, eggs in portal tracts of liver and bowel
  - heavy infections: intestinal polyps, portal and pulmonary HTN, splenomegalay (2° to portal HTN), hepatomegaly
- *S. hematobium*
  - worms in vesical plexus, eggs in distal ureter and bladder induce granulomas and fibrosis
  - hematuria and obstructive uropathy; associated with squamous cell bladder cancer
  - neurologic complications: spinal cord neuroschistosomiasis (transverse myelitis), cerebral or cerebellar neuroschistosomiasis (increased ICP, focal CNS signs, seizures)
  - pulmonary complications: granulomatous pulmonary endarteritis, pulmonary HTN, cor pulmonale; especially in patients with hepatosplenic involvement

**Figure 17. Life cycle of Schistosoma**
Ectoparasites

- scabies, lice
- see Dermatology, D28

Travel Medicine

General Travel Precautions
- vector-borne: long sleeves, long pants, hats, repellents (containing permethrin) applied to clothes, belongings, and bed nets, and skin repellents (such as DEET) applied to exposed skin
- food/water: avoid eating raw meats/seafood, uncooked vegetables, and milk/dairy products; drink only bottled beverages, chlorinated water, boiled water
- recreation: caution when swimming in schistosomiasis-endemic regions (Lake Malawi), fresh water rafting/kayaking, beaches that may contain human/animal waste products, near storm drains, after heavy rains
- prophylaxis: malaria (chloroquine, mefloquine, atovaquone + proguanil, doxycycline), traveller’s diarrhea (bismuth salicylate)
- standard vaccines up to date (hepatitis B, MMR, tetanus/diphtheria, varicella, pertussis, polio, influenza)
- travel vaccines: hepatitis A/B, Japanese encephalitis, typhoid fever, ETEC, cholera
- sexually transmitted and blood-borne infections: safe sex practices, avoidance of percutaneous injury through razors, tattoos, piercings

Infectious Diseases to Consider
- vector borne: malaria, dengue fever, Chikungunya fever, yellow fever, spotted fever rickettsioses, West Nile virus, trypanosomiasis, Japanese encephalitis, tick-borne encephalitis, leishmaniasis
- sexually transmitted: HIV, HBV, acute HSV, syphilis, usual STIs
- zoonotic: rabies, hantavirus, tularemia, Q fever, anthrax, brucellosis
- orally transmitted: HBV, HEV, acute HSV, typhoid fever, paratyphoid, amoebiasis, dysentery
- airborne: TB
- food/water: HAV, HEV, Brucella, Salmonella, Shigella, Giardia, listeria, cryptosporidium, cyclospora
- soil/water: schistosomiasis, strongyloidiasis, leptospirosis, cutaneous larva migrans, histoplasmosis, paracoccidioidomycosis

Fever in the Returned Traveller

Etiology
- commonly identified causes of fever in returning traveller
  - parasitic: malaria (20-30%)
  - viral: non-specific mononucleosis-like syndrome (4-25%), dengue (5%), viral hepatitis (3%)
  - bacterial: typhoid from *Salmonella* (2-7%), rickettsioses (3%)
  - diverse group of causative pathogens: traveller’s diarrhea (10-20%), RTI (10-15%), UTI/STI (2-3%)
- febrile illness in travellers can be caused by routine infections that are common in nontravellers (e.g. URTI, UTI)
- less commonly, fever can be due to non-infectious causes (e.g. DVT, PE)

History
- pre-travel preparation
- travel itinerary: when, where, why, what, who, how?
  - dates of travel (determine incubation period)
  - season of travel: wet or dry
  - destination: country, region (urban or rural), environment (jungle, desert, etc.)
  - purpose of trip
• persons visiting friends and family more likely to be exposed to local population and pathogens
  ▪ style of travel: lodgings, camping, adventure travelling
  ▪ local population: sick contacts
  ▪ transportation: use of animals

• exposure history
  ▪ street foods, untreated water: increased risk of traveller’s diarrhea, enteric fever
  ▪ uncooked meat unpasteurized dairy: increased risk of parasitic infection
  ▪ body fluids (sexual contacts, tattoos, piercings, IVDU, other injections)
  ▪ increased risk of HBV, HCV, HIV, GC, C. trachomatis, syphilis
  ▪ animal/insect bites: increased risk of malaria, dengue, rickettsioses, rabies

• fever pattern
• incubation period: use the earliest and latest possible dates of exposure to narrow the differential diagnosis and exclude serious infections
  ▪ <21 d: consider malaria, typhoid fever, dengue fever, rickettsioses; exclude HBV, TB
  ▪ >21 d: consider malaria, TB; exclude dengue fever, traveller’s diarrhea, rickettsioses

• body systems affected: GI, respiratory, CNS, skin

Investigations
• all travellers with fever should undergo the following tests
  ▪ blood work: CBC and differential, liver enzymes, creatinine, thick and thin blood smears x3 (for malaria), blood C&S
  ▪ urine: urinalysis, urine C&S if dysuria or other localizing signs
• special tests based on symptoms, exposure history, and geography
  ▪ stool: C&S, O&P
  ▪ CXR
  ▪ dengue serology for IgM

Table 28. Fever in the Returned Traveller

<table>
<thead>
<tr>
<th>Illness</th>
<th>Geography/Timing</th>
<th>Pathogen</th>
<th>Incubation Period</th>
<th>Clinical Manifestations</th>
<th>Diagnosis</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Africa, C. and S. America, SE Asia</td>
<td><em>Plasmodium falciparum</em>, <em>Plasmodium vivax</em>, <em>P. malariae</em>, <em>P. knowlesi</em></td>
<td>10 d to 40 yr</td>
<td>Fever and flu-like illness, (shaking chills, H/A, muscle aches, and fatigue) N/V and diarrhea Anaemia and jaundice</td>
<td>Blood smear (thick and thin) x3 Antigen detection PCR (mostly a research tool)</td>
<td>Artesunate (for severe disease) + malarone, doxycycline, or clindamycin Quinine sulfate + doxycycline or clindamycin Chloroquine + primaquine</td>
</tr>
<tr>
<td>Dengue</td>
<td>South East Asia, Caribbean</td>
<td>Dengue viruses</td>
<td>3 d to 2 wk</td>
<td>Sudden onset of fever, H/A, retro-orbital pain, myalgias, and arthralgias Leukopenia Thrombocytopenia Hemorrhagic manifestations (rare in travellers)</td>
<td>Anti-dengue IgM positivity</td>
<td>Symptom relief: Acetaminophen (avoid using NSAIDs because of anticoagulant properties)</td>
</tr>
<tr>
<td>Typhoid (enteric fever)</td>
<td>Global but mostly Indian subcontinent</td>
<td><em>Salmonella typhi</em>, <em>Salmonella paratyphi</em></td>
<td>3 to 60 d</td>
<td>Sustained fever 39°-40°C (103°-104°F) Abdominal pain, H/A, loss of appetite, cough, constipation</td>
<td>Stool, urine, or blood sample positive for S. typhi or S. paratyphi</td>
<td>Quinolone antibiotic (e.g. ciprofloxacin), ceftriaxone, or macrolide</td>
</tr>
<tr>
<td>Tick Typhus</td>
<td>Mediterranean, South Africa, India</td>
<td><em>Rickettsia</em></td>
<td>1 to 2 wk</td>
<td>Fever, H/A, fatigue, muscle aches, occasionally rash Eschar at site of tick bite Thrombocytopenia Elevated liver enzymes</td>
<td>Serology Presence of classic tick eschar</td>
<td>Doxycycline</td>
</tr>
<tr>
<td>TB</td>
<td>Global</td>
<td><em>M. tuberculosis</em></td>
<td>Variable</td>
<td>Fever, cough, hemoptysis</td>
<td>CXR Sputum culture and acid-fast stain</td>
<td>Ethambutol, isoniazid, pyrazinamide, rifampin</td>
</tr>
<tr>
<td>Mononucleosis</td>
<td>Caribbean, C. and S. America</td>
<td>EBV or CMV</td>
<td>30 to 50 d</td>
<td>Malaise, fatigue, pharyngitis, lymphadenopathy, splenomegaly</td>
<td>Atypical lymphocytes on blood smear and positive heterophilic antibody (monospot) test</td>
<td>Acetaminophen or NSAIDs, fluids</td>
</tr>
</tbody>
</table>
**Fever of Unknown Origin**

**Table 29. Classification of Fever of Unknown Origin (FUO) – Temp >38.3°C/101°F on several occasions**

<table>
<thead>
<tr>
<th>Classical FUO</th>
<th>Nosocomial FUO</th>
<th>Neutropenic FUO</th>
<th>HIV-associated FUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration &gt;3 wk</td>
<td>Hospitalized patient</td>
<td>Neutrophil count &lt;500/mL or is expected to fall to that level in 1-2 d</td>
<td>HIV infections</td>
</tr>
<tr>
<td>Infection not present/ incubating on admission</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
<td>Duration &gt;4 wk for outpatients, &gt;3 d for hospitalized patients</td>
</tr>
<tr>
<td>Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation</td>
<td>Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation</td>
<td>Diagnosis uncertain after 3 outpatient visits or 3 d in hospital or 1 wk of intensive ambulatory investigation</td>
<td>Diagnosis uncertain after 3 d of investigation, including at least 2 d incubation of cultures</td>
</tr>
</tbody>
</table>

**Etiology of Classic FUO**
- Infectious causes (~30%)
  - TB: extra-pulmonary (most common), miliary, pulmonary (if pre-existing disease)
  - Abscess: subphrenic, liver, splenic, pancreatic, perinephric, diverticular, pelvis, psoas
  - Osteomyelitis
  - Bacterial endocarditis (culture negative)
  - Uncommon: viral (CMV, EBV), fungal (histoplasmosis, cryptococcosis), parasitic (toxoplasmosis, leishmaniasis, amoebiasis, malaria)
- Neoplastic causes (~20%)
  - Most commonly lymphomas (especially non-Hodgkin’s) and leukemias, also multiple myeloma, myelodysplastic syndrome
  - Solid tumours: RCC (most common), also breast, liver ( hepatoma), colon, pancreas, or liver metastases
- Collagen vascular diseases (~30%)
  - SLE, RA, rheumatic fever, vasculitis (temporal arteritis, PAN), JRA, Still’s disease
- Miscellaneous (~20%)
  - Drugs, factitious fever
  - Sarcoidosis, granulomatous hepatitis, IBD
  - Hereditary periodic fever syndromes (such as familial Mediterranean fever)
  - Venous thromboembolic disease: PE, DVT
  - Endocrine: thyroiditis, thyroid storm, adrenal insufficiency, pheochromocytoma
- Unknown in 30-50% despite detailed workup

**Approach to Classic FUO**
- Careful history: travel, environmental/occupational exposures, infectious contacts, medication history, immunizations, TB history, sexual history, past medical history, comprehensive review of systems (including symptoms that resolved before interview)
- Thorough physical exam: fever pattern, rashes (skin, mucous membranes), murmurs, arthritis, lymphadenopathy, organomegaly
- Initial investigations as appropriate
  - Blood work: CBC and differential, electrolytes, BUN, Cr, calcium profile, LFTs, ESR, CRP, muscle enzymes, RF, ANA, serum protein electrophoresis (SPEP), blood smear
  - Cultures: blood (x2 sets), urine, sputum, stool C&S, O&P, other fluids as appropriate
  - Serology: HIV, monospot, CMV IgM
  - Imaging: CXR, abdominal imaging
- If there are diagnostic clues from any of the above steps, proceed with directed exam, biopsies or invasive testing as required, followed by directed treatment once a diagnosis is established
- If no diagnosis with the above, consider empiric therapy vs. watchful waiting
  - Without intervention: patients that remain undiagnosed despite extensive workup have good prognosis

**Causes of Nosocomial FUO**
- B, C, D, E
  - Bacterial and fungal infections of respiratory tract and surgical sites
  - Catheters (intravascular and urinary)
  - Drugs
  - Emboli

**Drugs that may Cause Fever**
- Anti-microbials (sulfonamides, penicillins, nitrofurantoin, antimalarials)
- Anti-hypertensives (hydralazine, methyldopa)
- Anti-epileptics (barbiturate, phenytoin)
- Anti-arythmics (quinine, procainamide)
- Anti-inflammatory (NSAIDs)
- Anti-thrombotics (ASA)
- Anti-histamines
- Anti-thyroid
Infections in the Immunocompromised Host

- Immunocompromised hosts have increased susceptibility to infections from pathogens that are typically low virulence, commensal, or latent
- Type of immunodeficiency predicts probable spectrum of agents

Factors that Compromise the Immune System
- General: age (very young or elderly), malnutrition
- Immune disease: HIV/AIDS, malignancies, asplenia (functional or anatomic), hypogammaglobulinemia, neutropenia
- DM
- Iatrogenic: corticosteroids, chemotherapy, radiation treatment, anti-TNF therapy, other immunosuppressive drugs (e.g. in transplant patients)

Table 30. Types of Immunodeficiency

<table>
<thead>
<tr>
<th>Type</th>
<th>Conditions</th>
<th>Vulnerable To</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cell-Mediated Immunity</td>
<td>HIV, Hodgkin’s, hairy cell leukemia, cytotoxic drugs, SCID, DiGeorge syndrome</td>
<td>Latent viruses, Fungi, Parasites</td>
</tr>
<tr>
<td>Humoral Immunity</td>
<td>CLL, lymphosarcoma, multiple myeloma, nephrotic syndrome, protein-losing enteropathy, burns, sickle cell anemia, asplenia, splenectomy, selective Ig deficiencies, Wiskott-Aldrich syndrome</td>
<td>Encapsulated organisms (S. pneumoniae, H. influenzae, N. meningitidis, Salmonella typhi, GBS)</td>
</tr>
<tr>
<td>Neutrophil Function</td>
<td>Myelodysplasia, paroxysmal nocturnal hemoglobinuria, radiation, cytotoxic drug therapy, C3 or C5 deficiencies, chronic granulomatous disease</td>
<td>Catalase-producing organisms (Staphylococcus, Serratia, Nocardia, Aspergillus)</td>
</tr>
</tbody>
</table>

Febrile Neutropenia

Definition
- Fever (≥38.3°C/101°F or ≥38.0°C/100.4°F for ≥1 h) and one of
  - ANC <0.5 OR
  - ANC <1.0 but trending down to 0.5

Pathophysiology
- Decreased neutrophil production
  - Marrow: infection, aplastic/myelophthisic anemia, leukemia, lymphoma, myelodysplastic syndromes
  - Iatrogenic: cancer chemotherapy, radiation, drugs
  - Deficiencies: vitamin B12, folate
- Increased peripheral neutrophil destruction
  - Autoimmune: Felty’s syndrome, SLE, antineutrophil antibodies
  - Splenic sequestration

Epidemiology/Etiology
- Most common life-threatening complication of cancer therapy
- 8 cases per 1,000 cancer patients per yr in the U.S.
- Causative organism identified only 1/3 of the time
- GN (especially Pseudomonas) historically most common
- GP more common now
- Fungal superinfection if neutropenia prolonged or if concurrent antibiotic use (especially Candida, Aspergillus)

Investigations
- Examine for potential sites of infection: mucositis and line infections are most common
- Do NOT perform DRE; examine perianal region
- Blood C&S (x2 sets), urine C&S, culture all indwelling catheter ports, ± sputum C&S and NP swab for respiratory viruses
- CBC and differential, Cr, BUN, electrolytes, AST/ALT, total bilirubin

Treatment
- Most hospitals have their own specific protocol; one example is presented below

ANC (absolute neutrophil count) = WBC x (%neutrophils + %bands)

Usual signs and symptoms of infection may be diminished because neutrophils are required for a robust inflammatory response; exam and x-ray findings may be more subtle.

WBC is lowest between 5-10 d after last chemotherapy cycle

Prophylaxis against FN with G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) decreases hospitalization without affecting mortality (indicated if risk of FN 20% or if FN has occurred in a previous chemotherapy cycle)
Infections in Solid Organ Transplant Recipients

- infection is a leading cause of early morbidity/mortality in transplant recipients
- infection depends on degree of immunosuppression
- common infections <1 mo post-transplant
  - bacterial infection of wound/lines/lungs, herpetic stomatitis
- common infections >1 mo post-transplant
  - viral (especially CMV, EBV, VZV)
  - fungal (especially Aspergillus, Cryptococcus, P. jiroveci)
  - protozoan (especially Toxoplasma)
  - unusual bacterial/mycobacterial infections (especially TB, Nocardia, Listeria)

Prophylactic Vaccinations Given Before Transplant
- to all transplant patients: DTaP, pneumococcal, influenza, hepatitis A and B vaccines
- if low titre or poor documentation: MMR, polio, varicella vaccination (with booster 4-8 wk later)

Immune Reconstitution Syndrome

Definition
- a harmful inflammatory response directed against a previously acquired infection following a recovery of the immune system

Etiology
- paradoxical worsening of a successfully or partially treated opportunistic infection
- new onset response to a previously unidentified opportunistic infection
- the majority of cases are in HIV/AIDS or immunosuppressed patients starting anti-retroviral therapy or discontinuing immunosuppressive therapy; sudden recovery from an immunosuppressive state towards a pro-inflammatory state directed towards subclinical infection results in fever and inflammation
- can occur in response to multiple infections
  - Mycobacteria (tuberculosis, avium complex)
  - Cryptococcus
  - Pneumocystis
  - Toxoplasma
  - HBV and HCV
  - Herpes viruses (VZV reactivation, HSV, CMV)
  - JC virus (progressive multifocal leukoencephalopathy)
  - Molluscum contagiosum
**A Simplified Look at Antibiotics**

- general overview, see Table 31 for more details

1. Penicillins

   ![Penicillin G (IV)/Penicillin V (PO)
   (most Streptococci, N. meningitidis, many oral anaerobes except B. fragilis)
   Ampicillin (IV)/Amoxicillin (PO)
   + Enterococcus and H. influenzae, Proteus, Listeria, E. coli, Salmonella, Shigella
   Amoxicillin-clavulanate
   + β-lactamase producing organisms including anaerobes
   Piperacillin
   + Pseudomonas and Enterobacter
   Piperacillin/tazobactam
   + β-lactamase producing organisms including anaerobes
   Cloxacillin
   + MSSA but 4 Streptococci

   **Figure 19. Penicillins**

2. Cephalosporins (PO/IV)
   - 1st generation: cephalexin/cefazolin (mostly GP, some GN)
   - 2nd generation: cefuroxime/cefprozil (some GP and some GN, *anaerobes)
   - 3rd generation: cefixime/cefotaxime, ceftriaxone (good Streptococcal coverage, mostly GN), and cefazidime (no GP, mostly GN, *Pseudomonas*)
   - 4th generation: --/cefepime (most GP, most GN, *Pseudomonas*)

3. Aminoglycosides (GN aerobic bacilli)
   - gentamicin
   - tobramycin
   - amikacin

   - erythromycin
   - clarithromycin
   - azithromycin

5. Fluoroquinolones (GN – although resistance becoming a huge problem)
   - ciprofloxacin (+ *Pseudomonas*)
   - norfloxacin (for UTI only)
   - respiratory fluoroquinolones (some GP, GN, "atypicals", *Legionella, Mycoplasma, Chlamydia phila, Mycobacteria*)
   - levofloxacin
   - moxifloxacin (+ anaerobes)
6. Carbapenems (broad coverage: GP, GN, and anaerobes)
- imipenem (+ Pseudomonas)
- meropenem (+ Pseudomonas)
- ertapenem

7. Others
- doxycycline/tetracycline (GP, syphilis, Chlamydia phila, Rickettsia, Mycoplasma)
- tigecycline (for resistant GP infections, GN, anaerobes, Chlamydia phila, Rickettsia, Mycoplasma)
- vancomycin (all GP and C. difficile – the oral form)
- linezolid (for resistant GP infections)
- daptomycin (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most S. aureus including: MRSA, GN aerobes, Pneumocystis)
- nitrofurantoin (GN bacilli, S. saprophyticus, Enterococcus)
- linezolid (for resistant GP infections)
- daptomycin (for resistant GP infections)
- clindamycin (most GP, GN anaerobes)
- TMP/SMX (most S. aureus including: MRSA, GN aerobes, Pneumocystis)
- nitrofurantoin (GN bacilli, S. saprophyticus, Enterococcus)
- vancomycin (all GP and C. difficile – the oral form)
- linezolid (for resistant GP infections)
- treatment for C. difficile: metronidazole OR oral vancomycin; consider both in serious infection

**Antimicrobials**

**Antibiotics**

- empiric antibiotic therapy
  - choose antibiotic(s) to cover for most likely and lethal organisms for the type of infection prior to obtaining laboratory results (usually reserved for serious infections)
  - adjust antibiotic(s) based on C&S
    - if causative organism identified, use antibiotic to which organism is sensitive
    - if causative organism not identified, re-evaluate need for ongoing antimicrobial therapy (and continue with empiric antibiotic(s) if indicated)

**Reasons for Combination Therapy**
- Polymicrobial infection
- Empiric therapy pending culture results
- Synergy for difficult to treat pathogens (e.g. Enterococcus spp. causing endocarditis)
- To prevent emergence of resistance

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**Figure 20. Mechanism of action of antibiotics**
### Table 31. Antibiotics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Penicillins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzy1 pencillin - pencillin G IV/IM - pencillin V PO</td>
<td>GP except <em>Staphylococcus, Enterococcus, Oral anaerobes, Syphilis</em></td>
<td>Bactericidal; β-lactam inhibits cell wall synthesis by binding penicillin binding protein (PBP) preventing cross-linking of peptidoglycan</td>
<td>Immediate allergy (IgE): anaphylaxis, urticaria Late-onset allergy (IgG): urticaria, rash, serum sickness Interstitial nephritis Dose-related toxicity: seizures Diarrhea</td>
<td>Mild to moderately severe infections caused by susceptible organisms including <em>actinomycosis, streptococcal pharyngitis, streptococcal skin and soft tissue infections, pneumococcal pneumonia, syphilis</em></td>
<td>Hypersensitivity to penicillin</td>
</tr>
<tr>
<td>Aminopenicillin - ampicillin IV - amoxicillin PO (Amoxillin)</td>
<td>Same as penicillin AND <em>Enterococcus, Staphylococcus, Streptococcus</em></td>
<td>See above</td>
<td>See above</td>
<td>Bacterial meningitis and endocarditis (IV ampicillin), acute otitis media (ADOM), streptococcal pharyngitis, sinusitis, acute exacerbations of COPD, part of multidrug therapy for <em>H. pylori</em> treatment, Lyme disease, pneumococcal pneumonia; UTI (amoxicillin and ampicillin) for most <em>enterococci</em> and susceptible gram-negative pathogens</td>
<td>Hypersensitivity to penicillin or β-lactam antibiotics</td>
</tr>
<tr>
<td>Isoxazolyl penicillin - cloxacillin - methicillin - natcillin - oxacillin</td>
<td>Methicillin-sensitive <em>Staphylococcus aureus; Streptococcus</em></td>
<td>See above</td>
<td>See above</td>
<td>Bacterial infections caused by <em>staphylococci</em> and streptococci including skin soft-tissue infections</td>
<td>Hypersensitivity to cloxacillin or any penicillin</td>
</tr>
<tr>
<td>β-lactam/β-lactamase inhibitor combinations - amoxicillin-clavulanate (Clavulin), Augmentin, - piperacillin/tazobactam (Tazocin)</td>
<td>Same as penicillin AND <em>Staphylococcus, Enterococcus, Anaerobes (oral and gut)</em></td>
<td>β-lactamases produced by certain bacteria inactive β-lactams Lactamase inhibitors prevent this process, preserving antibacterial effect of β-lactams</td>
<td>See above</td>
<td>Various β-lactamase producing bacteria, <em>Clavulin</em> sensitive bacteria including RTI, sinusitis, AOM, skin and soft tissue infections, UTI, and severe intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to penicillin or cephalosporin History of <em>Clavulin</em> associated jaundice or hepatic dysfunction</td>
</tr>
<tr>
<td><strong>Cephalosporins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PO 1° cefazolin (Keflex)</td>
<td>IV cefazolin (Ancef)</td>
<td>GP Good with the exception of <em>Enterococcus</em> and MRSA</td>
<td>GN <em>E. coli, Klebsiella, Proteus, H. influenzae (not all isolates)</em></td>
<td>Bactericidal; β-lactam inhibits PBP, prevents cross-linking of peptidoglycan, less susceptible to penicillinases 10% penicillin allergy cross-reactivity Nephrotoxicity</td>
<td>Skin and soft tissue infections, prevention of surgical site infections (cefaizolin); infections caused by susceptible organisms (especially <em>Staph and Strep infections)</em></td>
</tr>
<tr>
<td>2° cefuroxime (Cefuroxim) - cefotaxime (Clavulin) - ceftriaxone (Rocephin)</td>
<td>cefuroxime (Zinacef) - cefotaxime (Claforan) - ceftriaxone (Fortaz)</td>
<td>Weaker activity than 1° More coverage than 1° (includes anaerobes)</td>
<td>See above</td>
<td>See above</td>
<td>Upper and lower respiratory tract infections, pneumococcal pneumonia; soft tissue infections</td>
</tr>
<tr>
<td>3° ceftriaxone (Rocephin) - cefotaxime (Claforan) - cefazidime (Forza)</td>
<td>S. aureus + streptococcal coverage (cefotaxime and ceftriaxone) especially <em>S. pneumoniae</em> Broad coverage (Includes <em>Pseudomonas</em> for cefazidime only)</td>
<td>See above</td>
<td>See above</td>
<td>~1% penicillin allergy cross-reactivity Community-acquired pneumonia (cefotaxime, ceftriaxone), gonorrhea (use ceftriaxone), community-acquired bacterial meningitis (ceftriaxone, cefotaxime); abdominal and pelvic infections (cefotaxime or ceftriaxone in combination with metronidazole); once-daily administration makes ceftriaxone convenient for outpatient IV therapy</td>
<td>Severe hypersensitivity (Type I) to other β-lactam antibiotics</td>
</tr>
<tr>
<td>4° cefepime (Maxipin)</td>
<td>Broad spectrum</td>
<td>Broad coverage including <em>Pseudomonas</em></td>
<td>See above</td>
<td>See above</td>
<td>Empiric therapy for febrile neutropenia</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CELL WALL INHIBITORS</strong></td>
<td></td>
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<tr>
<td><strong>Carbapenems</strong></td>
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<td></td>
</tr>
<tr>
<td>Imipenem (Primaxin®)</td>
<td>GP except MRSA GN including Pseudomonas + Enterobacter, ESBLs, anaerobes</td>
<td>-lactam inhibits PBP and prevents cross-linking of peptidoglycan</td>
<td>Penicillin allergy</td>
<td>Treatment of infections caused by GNB producing extended-spectrum -lactamases, serious infections caused by susceptible organisms</td>
<td>Hypersensitivity to imipenem</td>
</tr>
<tr>
<td>Meropenem (Merrem®)</td>
<td>See above; does not cover Enterococcus</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Hypersensitivity to -lactams</td>
</tr>
<tr>
<td>Ertapenem (Invanz®)</td>
<td>GP except Enterococcus, MRSA GN including Enterobacter (but not Pseudomonas), anaerobes</td>
<td>See above</td>
<td>See above</td>
<td>See above; once-daily administration makes it convenient for outpatient IV therapy</td>
<td>Hypersensitivity to -lactams</td>
</tr>
<tr>
<td><strong>Glycopeptides</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td>GP including MRSA, not VRE C. difficile if PO</td>
<td>Glycopeptide sterically inhibits cell wall synthesis</td>
<td>Red Man Syndrome Nephrotoxicity Ototoxicity Thrombocytopenia</td>
<td>Severe or life-threatening GP infections, patients with -lactam allergy May only be taken orally for severe C. difficile infection</td>
<td>Hypersensitivity to vancomycin</td>
</tr>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (50S RIBOSOME)</strong></td>
<td></td>
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<tr>
<td><strong>Macrolides</strong></td>
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</tr>
<tr>
<td>Erythromycin (Erybid®, Eryc®)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>“This agent is rarely used due to GI upset</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Clarithromycin (Biaxin®)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, skin infections, non-tuberculous mycobacterial infections, part of multidrug therapy for H. pylori treatment</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td>Azithromycin (Zithromax®)</td>
<td>See above</td>
<td>See above</td>
<td>See above</td>
<td>Susceptible RTI, acute exacerbations of COPD, community-acquired pneumonia, skin infections, Campylobacter infections if treatment indicated, chlamydia</td>
<td>Hypersensitivity to macrolides</td>
</tr>
<tr>
<td><strong>Lincosamides</strong></td>
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<td></td>
</tr>
<tr>
<td>Clindamycin (Dalacin®)</td>
<td>GP except Enterococcus, most community-acquired MRSA Anaerobes</td>
<td>Inhibits peptide bond formation at 50S ribosome</td>
<td>Pseudomembranous colitis GI upset</td>
<td>Treatment of suspected or proven infections caused by GP anaerobes including skin and skin structure infections, oropharyngeal infections, in combination with GN coverage for intra-abdominal and pelvic infections</td>
<td>Hypersensitivity to clindamycin Infants &lt; 30 d</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>GP GN Anaerobes</td>
<td>Inhibits peptidyl transferase action of tRNA at 50S ribosome</td>
<td>Aplastic anemia Grey Baby Syndrome</td>
<td>Serious infections by susceptible organisms when suitable alternatives are not available including meningococcal disease in patients with anaphylaxis to -lactams</td>
<td>Hypersensitivity to chloramphenicol</td>
</tr>
<tr>
<td>Linezolid (Zyvoxam®)</td>
<td>GP including VRE + MRSA</td>
<td>Binds 50S ribosome and prevents functional 70S initiation complex</td>
<td>HTN (acts as MAOI) Risks with prolonged use: myelosuppression optic neuropathy, peripheral neuropathy</td>
<td>Vancomycin-resistant Enterococcus faecium infections including intra-abdominal, skin and skin structure, and urinary tract infections, MRSA infections as outpatient therapy</td>
<td>Hypersensitivity to linezolid</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PROTEIN SYNTHESIS INHIBITORS (30S RIBOSOME)</strong></td>
<td></td>
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</tr>
<tr>
<td><strong>Aminoglycosides</strong></td>
<td></td>
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</tr>
<tr>
<td>gentamicin, tobramycin, amikacin (Amikin®)</td>
<td>GN (includes Pseudomonas)</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>Nephrotoxicity (reversible) Vestibular and ototoxicity (irreversible)</td>
<td>GN infections when alternatives do not exist, UTIs, used in low doses for synergy with β-lactams or with vancomycin for the treatment of serious enterococcal infections</td>
<td>Pre-existing hearing loss and renal dysfunction</td>
</tr>
<tr>
<td><strong>Tetracyclines</strong></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>tetracycline (Apo-Tetra®, Nu-Tetra®), minocycline (Minocin®), doxycycline (Doxycycline), tigecycline (Tygacil®)</td>
<td>GP Anaerobes &quot;Atypicals&quot;: Chlamyphila, Mycoplasma, Rickettsia, Borrelia burgdorferi Troponema Malana prophylaxis (doxycycline) Tigecycline has activity against MRSA, VRE, and ESBL-producing E. coli/K pneumoniae</td>
<td>Binds 30S subunit of ribosome inhibiting protein synthesis</td>
<td>GI upset</td>
<td>Rickettsial infections, Chlamyphila, acne (tetracycline, minocycline), PID (step-down), malaria prophylaxis (doxycycline)</td>
<td>Severe renal or hepatic dysfunction Pregnancy or lactation Children under 8 yr</td>
</tr>
<tr>
<td><strong>TOPOISOMERASE INHIBITORS</strong></td>
<td></td>
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</tr>
<tr>
<td>Fluoroquinolones (FQs)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®), norfloxacin (Apo-Norflox®), levofloxacin (Levaquin®), moxifloxacin (Avelox®)</td>
<td>Poor GP activity GN (includes Pseudomonas) Atypicals Moxifloxacin also covers many anaerobes</td>
<td>Inhibits DNA gyrase</td>
<td>H/A, dizziness Allergy Seizures Prolonged QT Dysglycemia (levofloxacin, moxifloxacin)</td>
<td>Upper and lower RTI (not ciprofloxacin unless susceptible organism isolated), UTI, prostatitis (not moxifloxacin), bone and joint infections for susceptible organisms, skin and soft tissue infections (levofloxacin, moxifloxacin), infectious diarrhea, meningococcal prophylaxis, intra-abdominal infections (moxifloxacin, ciprofloxacin in combination with metronidazole or clindamycin), febrile neutropenia prophylaxis (ciprofloxacin, levofloxacin) or ciproflaxin in combination with amoxicillin-clavulanate low management of &quot;low-risk&quot; febrile neutropenia</td>
<td></td>
</tr>
<tr>
<td><strong>OTHER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampin</td>
<td>GP cocci N. meningitidis H. influenzae Mycobacteria</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatic dysfunction, P450 enzyme induction</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections, endocarditis involving prosthetic valve or other prosthetic device infections in combination with other antibiotic agents, prophylaxis for those exposed to people with N. meningitidis or Hib meningitis</td>
<td>Jaundice Not to be used as monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>Metronidazole (Flagyl®)</td>
<td>Anaerobes Protozoa</td>
<td>Forms toxic metabolites in bacterial cell which damage microbial DNA</td>
<td>Disulfiram-type reaction with EtOH Seizures Peripheral neuropathy</td>
<td>Protozoal infections (trichomoniasis, amoebiasis, giardiasis), bacterial vaginosis, anaerobic bacterial infections</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>GP including MRSA and VRE</td>
<td>Hypothesized to bind to cell wall and form channels leading to intracellular K+ depletion</td>
<td>Skeletal muscle injury at high doses (elevated CPK) Peripheral neuropathy</td>
<td>Bacteremia, endocarditis, skin and soft tissue, and other infections due to resistant GP infections including MRSA and VRE</td>
<td>Known hypersensitivity</td>
</tr>
</tbody>
</table>
### Table 31. Antibiotics (continued)

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Indications</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-METABOLITE</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trimethoprim-Sulfamethoxazole (TMP/SMX)</strong> (Septra&lt;sup&gt;®&lt;/sup&gt;, Bactrim&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>GP, especially S. aureus (including most MRSA), GN: enteric, Nocardia, Other: Pneumocystis, Toxoplasmosis</td>
<td>Inhibits folic acid pathway (TMP inhibits DHFR and SMX competes with PABA)</td>
<td>Hepatitis Stevens-Johnson syndrome, Bone marrow suppression, Hyperkalemia (increases free levels of many drugs, including glyburide, warfarin)</td>
<td>Susceptible UTI, RTI, GI infections, skin and soft tissue infections caused by staphylococcal species, treatment and prophylaxis of P. jiroveci pneumonia</td>
<td>Hypersensitivity to TMP-SMX, sulfa drugs</td>
</tr>
<tr>
<td>nitrofurantoin (MacroBID&lt;sup&gt;®&lt;/sup&gt;, Macrodantin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Enterococcus, S. saprophyticus GN (coli/febr)</td>
<td>Reactive metabolites inhibit ribosomal protein synthesis</td>
<td>Cholestasis, hepatitis, Hemolysis if G6PD deficiency, Intestinal lung disease with chronic use</td>
<td>Lower UTI, not pyelonephritis or bacteremia</td>
<td>Hyperuricosuria, gout, renal failure</td>
</tr>
<tr>
<td><strong>ANTI-MYCOBACTERIALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isoniazid (INH)</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Hepatotoxicity, Hepatitis Drug-induced SLE, Peripheral neuropathy</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB</td>
<td>Drug-induced hepatitis or acute liver disease</td>
</tr>
<tr>
<td>rifampin (RIF)</td>
<td>Mycobacteria</td>
<td>Inhibits RNA polymerase</td>
<td>Hepatotoxicity P450 enzyme inducer Orange tears, saliva, urine</td>
<td>Part of multidrug treatment for active TB, alone for treatment of latent TB, part of multidrug treatment of other mycobacterial infections</td>
<td>Jaundice Not to be used monotherapy (except for prophylaxis)</td>
</tr>
<tr>
<td>ethambutol</td>
<td>Mycobacteria</td>
<td>Inhibits mycolic acid synthesis</td>
<td>Loss of central and colour vision</td>
<td>Part of multidrug treatment for active TB and other mycobacterial infections</td>
<td>Renal failure</td>
</tr>
<tr>
<td>pyrazinamide (PZA)</td>
<td>Mycobacteria</td>
<td>Unknown</td>
<td>Hepatotoxicity Gout Gastric irritation</td>
<td>Part of multidrug treatment for active TB</td>
<td>Severe hepatic damage or acute liver disease, Patients with acute gout</td>
</tr>
</tbody>
</table>

| **SULFONES** |          |                     |                 |             |                  |
| dapsone sulfoxone | M. leprae, P. jiroveci, Toxoplasma | Inhibit folic acid synthesis by competition with PABA | Rash Drug fever, Agranulocytosis | Part of multidrug treatment for M. leprae, part of treatment for P. jiroveci pneumonia (with TMP), P. jiroveci pneumonia prophylaxis, toxoplasmosis prophylaxis with pyrimethamine |                  |

### Table 32. Antibiotics for Selected Bacteria

<table>
<thead>
<tr>
<th>Pseudomonas</th>
<th>S. aureus</th>
<th>Enterococcus</th>
<th>H. influenzae</th>
<th>Anaerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin</td>
<td>cloxacillin (MSSA)</td>
<td>ampicillin</td>
<td>amoxicillin-clavulanate</td>
<td>metronidazole</td>
</tr>
<tr>
<td>gentamicin, tobramycin</td>
<td>1° cephalosporin (MSSA)</td>
<td>amoxicillin</td>
<td>2°/3° cephalosporin</td>
<td>clindamycin</td>
</tr>
<tr>
<td>piperacillin/tazobactam</td>
<td>clindamycin</td>
<td>vancomycin</td>
<td>macrolides (clarithromycin, azithromycin)</td>
<td>amoxicillin-clavulanate</td>
</tr>
<tr>
<td>ceftazidime</td>
<td>vancomycin</td>
<td>nitrofurantoin (lower UTI)</td>
<td>levofloxacin</td>
<td>clindamycin</td>
</tr>
<tr>
<td>cefepime</td>
<td>linezolid (including MRSA)</td>
<td>linezolid</td>
<td>moxifloxacin</td>
<td>cefoxitin</td>
</tr>
<tr>
<td>meropenem</td>
<td>daptomycin (including MRSA)</td>
<td>daptomycin for VRE</td>
<td>moxifloxacin</td>
<td>pipercillin/tazobactam</td>
</tr>
<tr>
<td>imipenem</td>
<td>tigecycline (including MRSA)</td>
<td>tigecycline for VRE</td>
<td>moxifloxacin</td>
<td>daptomycin</td>
</tr>
</tbody>
</table>

**Rifampin**
- Good adjunct for treating prosthetic device infection (bacterial biofilm)
- Always used in combination with other antibiotics to reduce emergence of resistance
# Antivirals

## Table 33. Antivirals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTI-HERPESVIRUS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>acyclovir</td>
<td>HSV-1, 2, VZV</td>
<td>Guanosine analog inhibits viral DNA polymerase</td>
<td>PO well-tolerated</td>
<td>Hypersensitivity to acyclovir or valacyclovir</td>
</tr>
<tr>
<td>valacyclovir (Valtrex®)</td>
<td></td>
<td></td>
<td>IV: nephrotoxicity, CNS</td>
<td></td>
</tr>
<tr>
<td>famciclovir (Famvir®)</td>
<td>HSV-1, 2, VZV</td>
<td>See above</td>
<td>H/A, nausea</td>
<td>Hypersensitivity to famciclovir or penciclovir</td>
</tr>
<tr>
<td>penciclovir</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ganciclovir (Cytovene®)</td>
<td>CMV, HSV-1, 2, VZV, HHV-6, EBV</td>
<td>See above</td>
<td>Heme: neutropenia, thrombocytopenia, anemia</td>
<td>Hypersensitivity to ganciclovir or valganciclovir</td>
</tr>
<tr>
<td>valganciclovir</td>
<td></td>
<td></td>
<td></td>
<td>Possible cross-hypersensitivity between acyclovir and valacyclovir</td>
</tr>
<tr>
<td>foscarnet</td>
<td>CMV, Acyclovir-resistant HSV, VZV</td>
<td>Pyrophosphate analog inhibits viral DNA polymerase</td>
<td>Nephrotoxicity</td>
<td>Hypersensitivity to foscarnet</td>
</tr>
</tbody>
</table>

## OTHER ANTIVIRALS

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>(pegylated) interferon-α-2a or-2b</td>
<td>Chronic hepatitis B or C HPV</td>
<td>Inhibits viral protein synthesis</td>
<td>&quot;Flu-like&quot; syndrome, Depression, Bone marrow suppression</td>
<td>Hypersensitivity to any interferon</td>
</tr>
<tr>
<td>ribavirin (Virazole®)</td>
<td>Chronic hepatitis C, RSV, Lassa fever</td>
<td>Guanosine analog with multiple postulated mechanisms of action</td>
<td>Hemolytic anemia, Rash, conjunctivitis, Highly teratogenic</td>
<td>Pregnancy, women who may become pregnant or their partners, Renal impairment</td>
</tr>
<tr>
<td>Cidofovir</td>
<td>Adenovirus, CMV retinitis, Acyclovir and foscarnet resistant HSV</td>
<td>Deoxyxycytidine analogue inhibits DNA synthetase</td>
<td>Nephrotoxicity (proximal tubule dysfunction)</td>
<td>Renal failure; probenecid can reduce renal toxicity</td>
</tr>
<tr>
<td>amantadine (Symmetrel®)</td>
<td>Influenza A and B: treatment and prophylaxis</td>
<td>Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation</td>
<td>GI: N/V, diarrhea</td>
<td></td>
</tr>
<tr>
<td>lamivudine (Epivir®)</td>
<td>Chronic hepatitis B, HIV</td>
<td>See HIV and AIDS, ID28</td>
<td>See HIV and AIDS, ID28</td>
<td></td>
</tr>
<tr>
<td>Tenofovir</td>
<td>Chronic hepatitis B, HIV</td>
<td>See HIV and AIDS, ID28</td>
<td>See HIV and AIDS, ID28</td>
<td></td>
</tr>
<tr>
<td>Neuraminidase inhibitors:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>zanamivir (Relenza®)</td>
<td>Influenza A and B: treatment and prophylaxis</td>
<td>Inhibits neuraminidase, an enzyme required for release of virus from infected cells and prevention of viral aggregation</td>
<td>GI: N/V, diarrhea</td>
<td></td>
</tr>
<tr>
<td>oseltamivir (Tamiflu®)</td>
<td></td>
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</tbody>
</table>

# Antifungals

## Table 34. Antifungals

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>POLYENES</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>amphotericin B</td>
<td>Endemic mycoses: Histoplasmosis, Blastomycosis, Coccidioidomycosis, Pulmonary: Aspergillosis, CNS: Cryptococcus</td>
<td>A polye ne antifungal: inserts into fungal cytoplasmic membrane causing altered membrane permeability and cell death</td>
<td>Nephrotoxicity, Hypo/hyperkalemia, Infusion reactions: chills, fevers, H/A, Peripheral phlebitis</td>
<td>Renal impairment</td>
</tr>
<tr>
<td>nystatin (oral, topical)</td>
<td>Candidiasis: mucocutaneous, GI, oral (thrush), vaginal</td>
<td>See above</td>
<td>GI: N/V, diarrhea, Highly toxic if given IV</td>
<td></td>
</tr>
<tr>
<td><strong>imidazoles</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>clotrimazole (Canesten®)</td>
<td>Oral and vulvovaginal candidiasis, Dermatomycoses</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Pruritis, skin irritation</td>
<td></td>
</tr>
<tr>
<td>miconazole (Monistat®, Micazole®)</td>
<td>Vulvovaginal candidiasis, Dermatomycoses</td>
<td></td>
<td>Vaginal burning</td>
<td></td>
</tr>
<tr>
<td><strong>imidazoles</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ketoconazole (Nizoral®)</td>
<td>Dermatomycoses, Seborheic dermatitis</td>
<td>Pruritis, skin irritation, GI nonspecific results in decreased androgen and testosterone synthesis</td>
<td>Cross-sensitivity with other azoles possible, Hepatic dysfunction, Pregnant women or those that may become pregnant</td>
<td></td>
</tr>
<tr>
<td>Class and Drugs</td>
<td>Coverage</td>
<td>Mechanism of Action</td>
<td>Adverse Effects</td>
<td>Contraindications</td>
</tr>
<tr>
<td>----------------</td>
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</tr>
<tr>
<td><strong>TRIAZoles</strong></td>
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<td></td>
</tr>
<tr>
<td>fluconazole (Diflucan®)</td>
<td>Candida infections (mucosal and invasive)</td>
<td>All azoles: inhibit ergosterol synthesis and thereby alter fungal cell membrane permeability</td>
<td>Elevated liver enzymes</td>
<td>Cross-sensitivity with other azoles unknown</td>
</tr>
<tr>
<td></td>
<td>Cryptococcal meningitis (step-down therapy)</td>
<td></td>
<td>GI nonspecific</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>itraconazole (Sporanox®)</td>
<td>Sporotrichosis</td>
<td></td>
<td>Elevated liver enzymes</td>
<td>Cross-sensitivity with other azoles unknown</td>
</tr>
<tr>
<td></td>
<td>Onychomycoses</td>
<td>Rash</td>
<td>GI nonspecific</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Endemic mycoses: Histoplasmosis Blastomycosis Coccidioidomycosis</td>
<td>HTN</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hyperkalemia Peripheral edema</td>
<td></td>
</tr>
<tr>
<td>voriconazole (Vfend®)</td>
<td>Aspergillosis Candidiasis</td>
<td>Visual disturbance (30%) Hepatotoxicity Cutaneous photosensitivity Cutaneous squamous cell carcinoma with long-term use in immunosuppressed patients Prolonged QT Periostitis Neurologic toxicity</td>
<td>Elevated liver enzymes H/A</td>
<td>Cross-sensitivity with other azoles unknown</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GI nonspecific</td>
<td></td>
</tr>
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<td></td>
</tr>
<tr>
<td>posaconazole (Posanol®, Noxafil®)</td>
<td>Candidiasis Aspergillosis Mucormycosis</td>
<td></td>
<td>Elevated liver enzymes</td>
<td>Coadministration of cisapride, ergot alkaloids, pimozide, quinidine, or sirolimus</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Prolonged QT</td>
<td></td>
</tr>
<tr>
<td><strong>ALLYlamines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>terbinafine (Lamisil®)</td>
<td>Dermatomycoses Onychomycoses</td>
<td>Inhibits enzyme needed for ergosterol synthesis</td>
<td>Rash, local irritation</td>
<td>Active liver disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>GI nonspecific, transaminits</td>
<td></td>
</tr>
<tr>
<td><strong>ECHINOCANDINS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>caspofungin micafungin anidulafungin</td>
<td>Refractory aspergillosis, candidemia (azole-resistant)</td>
<td>Inhibits 1-3 β-D-glucan synthesis (needed for fungal cell wall)</td>
<td>Hepatotoxicity Infusion and injection site reactions</td>
<td></td>
</tr>
</tbody>
</table>

Figure 21. Mechanism of action of antifungals
### Antiparasitics

#### Table 35. Antiparasitics

<table>
<thead>
<tr>
<th>Class and Drugs</th>
<th>Coverage</th>
<th>Mechanism of Action</th>
<th>Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIMALARIALS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chloroquine</td>
<td>Malaria: treatment of erythrocytic phase of all five species of Plasmodium that infect humans&lt;br&gt;Note: High resistance of <em>P. falciparum</em> and <em>P. vivax</em> in certain geographic areas</td>
<td>Inhibits parasite heme polymerase</td>
<td>CNS: blurred vision, retinopathy, dizziness&lt;br&gt;Non-specific GI (rare with prophylaxis)</td>
<td>Hypersensitivity to chloroquine or other 4-aminoquinolines&lt;br&gt;Retinal or visual field changes due to 4-aminoquinolines</td>
</tr>
<tr>
<td>quinine</td>
<td>Malaria: treatment of all five species of Plasmodium that infect humans, including chloroquine-resistant <em>P. falciparum</em></td>
<td></td>
<td>Cinchonism: ears (tinnitus, vertigo), eyes (visual disturbance), GI (N/V, diarrhea), CNS (H/A, fever)</td>
<td>Hypersensitivity to quinine, may have cross-sensitivity with quinidine&lt;br&gt;Patients with G6PD deficiency, tinnitus, optic neuritis, hypoglycemia, history of blackwater fever or thrombocytopenic purpura due to quinine use</td>
</tr>
<tr>
<td>mefloquine (Lariam®)</td>
<td>Malaria: prophylaxis</td>
<td></td>
<td>CNS/Psych: irritability, nightmares, psychoses, suicide, depression, seizures, H/A</td>
<td>History of seizures, psychosis, severe anxiety or depression</td>
</tr>
<tr>
<td>primaquine</td>
<td>Malaria: treatment of liver hypnozoites of <em>P. vivax</em> and <em>P. ovale</em>; prophylaxis of all Plasmodium spp.&lt;br&gt;Pneumocystis jiroveci (with clindamycin)</td>
<td>Interferes with mitochondrial function</td>
<td>Hemolytic anemia in G6PD deficient&lt;br&gt;GI upset (take with food)</td>
<td>GI nonspecific&lt;br&gt;G6PD deficiency&lt;br&gt;Concurrent or recent use of quinacrine&lt;br&gt;Pregnancy</td>
</tr>
<tr>
<td>atovaquone/proguanil (Malarone®)</td>
<td>Malaria: treatment and prophylaxis of <em>P. falciparum</em></td>
<td>Inhibits mitochondrial electron transport and dihydrofolate reductase</td>
<td>N/V, anorexia, diarrhea, abdominal pain (take with food)</td>
<td>Hypersensitivity to atovaquone or proguanil&lt;br&gt;Severe renal impairment</td>
</tr>
<tr>
<td>artemisinin derivatives (artemether, artesunate, etc.)</td>
<td>Malaria: treatment of all Plasmodium species&lt;br&gt;Severe malaria (IV artesunate)&lt;br&gt;Typically used in combination with a longer-acting agent from above</td>
<td>Binds iron, leading to formation of free radicals that damage parasite proteins</td>
<td>Transient neurologic deficits (nystagmus, balance disturbance)&lt;br&gt;Transient neutropenia (at high doses of oral artesunate)&lt;br&gt;Transient neutropenia (at high doses of oral artesunate)&lt;br&gt;Delayed hemolysis</td>
<td>Hypersensitivity to artemisinins</td>
</tr>
<tr>
<td><strong>OTHER ANTI-PROTOZOAL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>iodoquinol (Diodoquin®)</td>
<td>Amoebiasis: <em>E. histolytica</em>, <em>Dientamoeba fragilis</em>, <em>Balantidium coli</em>, <em>Blastocystis hominis</em>&lt;br&gt;Pneumocystis jiroveci (with clindamycin)</td>
<td>Contact amoebicide that acts in intestinal lumen by uncertain mechanism</td>
<td>GI: N/V, diarrhea, abdominal pain&lt;br&gt;CNS: H/A, seizures, encephalitis</td>
<td>Hypersensitivity to any 8-hydroxy-quinoline or iodine&lt;br&gt;Patients with hepatic damage or optic neuropathy&lt;br&gt;Pregnancy</td>
</tr>
<tr>
<td>metronidazole</td>
<td>Amoebiasis, <em>T. vaginalis</em>, giardiasis, <em>D. fragilis</em></td>
<td>See Antibiotics, ID48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitazoxanide</td>
<td>Cryptosporidium, giardiasis, cyclosporiasis</td>
<td>Interferes with parasite anaerobic metabolism</td>
<td>N/V, diarrhea, abdominal pain, H/A</td>
<td>Hypersensitivity to nitazoxanide</td>
</tr>
<tr>
<td><strong>ANTI-HELMINTHICS</strong></td>
<td></td>
<td></td>
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<tr>
<td>praziquantel</td>
<td>Schistosomiasis and other flukes&lt;br&gt;Tapeworms</td>
<td>Increases Ca^{2+} permeability of helminth cell membrane, causing paralysis and detachment</td>
<td>N/V, fever, dizziness</td>
<td>Ocular cysticercosis</td>
</tr>
<tr>
<td>albendazole</td>
<td>Intestinal roundworms&lt;br&gt;<em>Neurocysticercosis</em>&lt;br&gt;<em>Echinococcus</em> → Hydatid disease</td>
<td>Inhibits glucose uptake into susceptible parasites</td>
<td>Elevated liver enzymes&lt;br&gt;Alopecia&lt;br&gt;GI nonspecific&lt;br&gt;Agranulocytosis</td>
<td>Pregnancy&lt;br&gt;Ocular cysticercosis or intraventricular cysticercosis</td>
</tr>
<tr>
<td>mebendazole (Vermox®)</td>
<td>Intestinal roundworms: pinworm, whipworm, hookworm, roundworm (e.g. <em>Ascaris</em>)</td>
<td>Inhibits microtubule formation and glucose uptake</td>
<td>Nonspecific GI</td>
<td>Pregnancy, infants</td>
</tr>
<tr>
<td>ivermectin</td>
<td>Strongyloidiasis&lt;br&gt;Onchocerciasis&lt;br&gt;Scabies</td>
<td>Interferes with polarization of nerve and muscles cells in susceptible parasites leading to paralysis</td>
<td>Nausea, bloating, diarrhea, myalgias, lightheadedness, H/A</td>
<td>Hypersensitivity to ivermectin&lt;br&gt;Pregnancy</td>
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<tr>
<td>diethylcarbamazine</td>
<td><em>Wuchereria bancrofti</em>&lt;br&gt;<em>Loa loa</em></td>
<td></td>
<td>Anorexia, N/V, H/A, drowsiness, psychoses, retinal hemorrhage&lt;br&gt;Mazzotti reaction if inflicted with onchocerciasis</td>
<td>Pregnancy&lt;br&gt;Onchocerciasis</td>
</tr>
</tbody>
</table>
Quick Reference: Common Infections and Their Antibiotic Management

- see Family Medicine, FM52

References

Principles of Microbiology

Hawley LB. High yield microbiology and infectious diseases. Lippincott Williams & Wilkins, 2000.


Neurological Infections


Respiratory Infections


Cardiac Infections


Gastrointestinal Infections
Dupont HL. Bacterial diarrhea. NEJM 2009;361:1560-1569.

Gottlieb T, Husher CS. Diarrhea in adults (acute). Clinical Evidence 2011;02:901.


Thielman NM, Guentert RL. Acute infectious diarrhea. NEJM 2004;350:38-47.

Bone and Joint Infections


Systemic Infections


HIV and AIDS


Fungal Infections


Parasitic Infections

Infections in the Immunocompromised Host

Fever of Unknown Origin

Nosocomial Infections

Travel Medicine

Antimicrobials
MD Consult Drugs Online. Available from: http://home.mdconsult.com/das/drugs/.

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Medical Imaging

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Magnetic Resonance Imaging
Positron Emission Tomography Scans
Contrast Enhancement

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Chest X-Ray
Computed Tomography Chest
Lung Abnormalities
Pulmonary Vascular Abnormalities
Pleural Abnormalities
 Mediastinal Abnormalities
Tubes, Lines, and Catheters

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Abdominal X-Ray
Approach to Abdominal X-Ray
Approach to Abdominal Computed Tomography
Contrast Studies
Specific Visceral Organ Imaging
“itis” Imaging
Angiography of Gastrointestinal Tract

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Gynecological Imaging
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Bone

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Nonvascular Interventions

Breast Imaging

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Breast Interventional Procedures
Breast Findings

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Acronyms

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<th>Term</th>
<th>Description</th>
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<tr>
<td>18FDG</td>
<td>18-fluorodeoxyglucose</td>
</tr>
<tr>
<td>AP</td>
<td>anteroposterior</td>
</tr>
<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AV</td>
<td>arteriovenous</td>
</tr>
<tr>
<td>AXR</td>
<td>abdominal x-ray</td>
</tr>
<tr>
<td>B dop</td>
<td>bronchiolitis obliterans</td>
</tr>
<tr>
<td>CNS</td>
<td>central nervous system</td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>computed tomography</td>
</tr>
<tr>
<td>CTA</td>
<td>computed tomographic angiogram</td>
</tr>
<tr>
<td>CVD</td>
<td>collagen vascular disease</td>
</tr>
<tr>
<td>CVR</td>
<td>central venous pressure</td>
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<tr>
<td>CXR</td>
<td>chest x-ray</td>
</tr>
<tr>
<td>DEXA</td>
<td>dual-energy x-ray absorptiometry</td>
</tr>
<tr>
<td>DSA</td>
<td>digital subtraction angiography</td>
</tr>
<tr>
<td>DTPA</td>
<td>diethylene triamine pentaacetic acid</td>
</tr>
<tr>
<td>DWI</td>
<td>diffusion-weighted image</td>
</tr>
<tr>
<td>ERCP</td>
<td>endoscopic retrograde cholangiopancreatography</td>
</tr>
<tr>
<td>FLAIR</td>
<td>fluid-attenuated inversion recovery</td>
</tr>
<tr>
<td>GI</td>
<td>gastrointestinal</td>
</tr>
<tr>
<td>GPA</td>
<td>granulomatosis with polyangiitis</td>
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<tr>
<td>HCC</td>
<td>hepatocellular carcinoma</td>
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<tr>
<td>HIDA</td>
<td>hepatobiliary iminodiacetic acid</td>
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<td>HVPAD</td>
<td>hexamethylpropyleneamine oxime</td>
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<tr>
<td>HSG</td>
<td>hysterosalpingogram</td>
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<tr>
<td>IBD</td>
<td>inflammatory bowel disease</td>
</tr>
<tr>
<td>ICV</td>
<td>intracerebral vascular disease</td>
</tr>
<tr>
<td>IPP</td>
<td>interstitial pulmonary fibrosis</td>
</tr>
<tr>
<td>IVP</td>
<td>intravenous pyelogram</td>
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<tr>
<td>KUB</td>
<td>kidneys, ureters, bladder</td>
</tr>
<tr>
<td>LA</td>
<td>left atrium</td>
</tr>
<tr>
<td>LV</td>
<td>left ventricle</td>
</tr>
<tr>
<td>MAA</td>
<td>microaggregated albumin</td>
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<tr>
<td>MAG3</td>
<td>middle cerebral artery</td>
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<td>MR</td>
<td>magnetic resonance</td>
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<td>MRA</td>
<td>magnetic resonance angiography</td>
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<td>MRCP</td>
<td>magnetic resonance cholangiopancreatography</td>
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<tr>
<td>MS</td>
<td>multiple sclerosis</td>
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<tr>
<td>MUGA</td>
<td>multiple gated acquisition</td>
</tr>
<tr>
<td>PA</td>
<td>posterioranterior</td>
</tr>
<tr>
<td>PBD</td>
<td>percutaneous biliary drainage</td>
</tr>
<tr>
<td>PET</td>
<td>positron emission tomography</td>
</tr>
<tr>
<td>PFT</td>
<td>pulmonary function test</td>
</tr>
<tr>
<td>PCC</td>
<td>peripherally-inserted central catheter</td>
</tr>
<tr>
<td>POCUS</td>
<td>point-of-care ultrasound</td>
</tr>
<tr>
<td>PTA</td>
<td>percutaneous transluminal angioplasty</td>
</tr>
<tr>
<td>PTC</td>
<td>percutaneous transhepatic cholangiography</td>
</tr>
<tr>
<td>RA</td>
<td>right atrium</td>
</tr>
<tr>
<td>RAIU</td>
<td>radioactive iodine uptake</td>
</tr>
<tr>
<td>RV</td>
<td>right ventricle</td>
</tr>
<tr>
<td>SPECT</td>
<td>single photon emission computed tomography</td>
</tr>
<tr>
<td>SVC</td>
<td>superior vena cava</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>TNK</td>
<td>tenecteplase</td>
</tr>
<tr>
<td>TP</td>
<td>tissue plasminogen activator</td>
</tr>
<tr>
<td>TRUS</td>
<td>transrectal ultrasound</td>
</tr>
<tr>
<td>TVUS</td>
<td>transvaginal ultrasound</td>
</tr>
<tr>
<td>US</td>
<td>ultrasound</td>
</tr>
<tr>
<td>VCU</td>
<td>voiding cystourethrogram</td>
</tr>
<tr>
<td>V/Q</td>
<td>ventilation/perfusion</td>
</tr>
</tbody>
</table>
Imaging Modalities

X-Ray Imaging
- X-rays, or Röentgen rays, are a form of electromagnetic energy of short wavelength
- As x-ray photons traverse matter, they can be absorbed (a process known as “attenuation”) and/or scattered
- The density of a structure determines its ability to attenuate or “weaken” the x-ray beam
  - Air < fat < water < bone < metal
- Structures that have high attenuation (e.g. bone) appear white on the resulting images

Plain Films
- X-rays pass through the patient and interact with a detection device to produce a 2-dimensional projection image
- Structures closer to the film appear sharper and less magnified
- Contraindications: pregnancy (relative)
- Advantages: inexpensive, non-invasive, readily available, reproducible, fast
- Disadvantages: radiation exposure, generally poor at distinguishing soft tissues

Fluoroscopy
- Continuous x-rays used for guiding angiographic and interventional procedures, in contrast examinations of the GI tract, and in the OR for certain surgical procedures (e.g. orthopedic, urological)
- On the fluoroscopic image, black and white are reversed so that bone and contrast agents appear dark and radiolucent structures appear light
- Advantages: allows for real-time visualization of structures
- Disadvantages: increased radiation dose; however, the use of pulsed fluoroscopy has reduced fluoroscopy time by 76% and radiation dose by 64% as compared with continuous fluoroscopy

Computed Tomography
- X-ray beam opposite a detector moves in a continuous 360° arc as patient is advanced through the imaging system
- Subsequent computer assisted reconstruction of anatomical structures from the axial plane
- Attenuation is quantified in Hounsfield units:
  - Subsequent computer assisted reconstruction of anatomical structures from the axial plane
  - Adjusting the “window width” (range of Hounsfield units displayed) and “window level” (midpoint value of the window width) can maximize visualization of certain anatomical structures (e.g. CT chest can be viewed using “lung”, “soft tissue”, and “bone” settings)
- Contraindications: pregnancy (relative), contraindications to contrast agents (e.g. allergy, renal failure)
- Advantages: delineates surrounding soft tissues, excellent at delineating bones and identifying lung/liver masses, may be used to guide biopsies, spiral/helical multidetector CT has fast data acquisition and allows 3D reconstruction, CTA is less invasive than conventional angiography
- Disadvantages: high radiation exposure, soft tissue characterization is not as good in comparison with MRI, IV contrast injection, anxiety of patient when going through scanner, higher cost, and less available than plain film

Ultrasound
- High frequency sound waves are transmitted from a transducer and passed through tissues; reflections of the sound waves are picked up by the transducer and transformed into images
  - Reflection (or “echo”) occurs when the sound waves pass through tissue interfaces of different acoustic densities
  - Structures are described based on their echogenicity: hyperechoic structures appear bright (U/S reflected) whereas hypoechoic structures appear dark (U/S waves not reflected back but pass through)
  - Higher U/S frequencies result in greater resolution but greater attenuation (i.e. deeper structures more difficult to visualize)
  - Artifacts: acoustic shadowing refers to the echo-free area located behind an interface that strongly reflects (e.g. tissue/bone) or absorbs (e.g. tissue/bone) sound waves; enhancement refers to the increase in reflection amplitude (i.e. increased brightness) from objects that lie below a weakly attenuating structure (e.g. cyst)
  - Duplex scan: grey-scale image that utilizes the Doppler effect to visualize the velocity of blood flow past the transducer
  - Colour Doppler: assigns a color based on the direction of blood flow
  - Advantages: relatively low cost, non-invasive, no radiation, real time imaging, may be used for guided biopsies, many different imaging planes (axial, sagittal), determines cystic versus solid
  - Disadvantages: highly operator-dependent, air in bowel may prevent imaging of midline structures in the abdomen, may be limited by patient habitus, poor for bone evaluation

Attenuation
- Bone (= bright) > grey matter > white matter (“fatty” myelin) > CSF > air (= dark)

Typical Effective Doses from Diagnostic Medical Examinations (in adults)*

<table>
<thead>
<tr>
<th>Procedure Type</th>
<th>Equivalent Period of Natural Background Radiation** (~3 mSv/yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-Ray</td>
<td></td>
</tr>
<tr>
<td>Skull</td>
<td>5 d</td>
</tr>
<tr>
<td>Cervical spine</td>
<td>10 wk</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>50 wk</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>75 wk</td>
</tr>
<tr>
<td>Chest (PA film)</td>
<td>1 d</td>
</tr>
<tr>
<td>Shoulders</td>
<td>0.5 d</td>
</tr>
<tr>
<td>Mammoscopy</td>
<td>20 wk</td>
</tr>
<tr>
<td>Abdomen</td>
<td>35 wk</td>
</tr>
<tr>
<td>Hip</td>
<td>35 wk</td>
</tr>
<tr>
<td>Pelvis</td>
<td>30 wk</td>
</tr>
<tr>
<td>Knee</td>
<td>0.25 d</td>
</tr>
<tr>
<td>F/U</td>
<td>150 yr</td>
</tr>
<tr>
<td>Dual-energy x-ray absorptiometry (without/with CT)</td>
<td>0.5/2 d &lt; 1 d/4 d</td>
</tr>
<tr>
<td>Upper GI series</td>
<td>300 yr</td>
</tr>
<tr>
<td>Small bowel series</td>
<td>250 yr</td>
</tr>
<tr>
<td>Barium enema</td>
<td>400 yr</td>
</tr>
<tr>
<td>CT</td>
<td></td>
</tr>
<tr>
<td>Head</td>
<td>100 yr</td>
</tr>
<tr>
<td>Neck</td>
<td>150 yr</td>
</tr>
<tr>
<td>Spine</td>
<td>300 yr</td>
</tr>
<tr>
<td>Chest</td>
<td>350 yr</td>
</tr>
<tr>
<td>Chest (pulmonary embolism)</td>
<td>750 yr</td>
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<tr>
<td>Coronary angiography</td>
<td>800 yr</td>
</tr>
<tr>
<td>Abdomen</td>
<td>400 yr</td>
</tr>
<tr>
<td>Pelvis</td>
<td>300 yr</td>
</tr>
<tr>
<td>Sodium 133Xe ventilation test</td>
<td>705 yr</td>
</tr>
<tr>
<td>Sodium 123I thyroid</td>
<td>315 yr</td>
</tr>
<tr>
<td>Thyrud 99mTc</td>
<td>240 yr</td>
</tr>
<tr>
<td>Thyroid 131I</td>
<td>95 yr</td>
</tr>
<tr>
<td>Cardiac rest stress test</td>
<td>470 yr</td>
</tr>
<tr>
<td>Lung ventilation</td>
<td>25 yr</td>
</tr>
<tr>
<td>Lung perfusion</td>
<td>100 yr</td>
</tr>
<tr>
<td>Renal 99mTc</td>
<td>90-165 yr</td>
</tr>
<tr>
<td>Liver-spleen 125I</td>
<td>105 yr</td>
</tr>
<tr>
<td>Bilary tract 99mTc</td>
<td>155 yr</td>
</tr>
</tbody>
</table>

*Source: Radiology 2008;248:254-263
**Calculated using average natural background exposure in Canada (Health Canada: http://www.hc-sc.gc.ca/hsf/rx/yh-uv/env/environ/espas-eng.php)
Magnetic Resonance Imaging

- non-invasive technique that does not use ionizing radiation
- able to produce images in virtually any plane
- patient is placed in a magnetic field; protons (H\(^+\)) align themselves along the plane of magnetization due to intrinsic polarity. A pulsed radiofrequency beam is subsequently turned on which deflects all the protons off their aligned axes due to absorption of energy from the radiofrequency beam. When the radiofrequency beam is turned off, the protons return to their pre-excitation axis, giving off the energy they absorbed. This energy is measured with a detector and interpreted by a computer to generate MR images
- the MR image reflects the signal intensity picked up by the receiver. This signal intensity is dependent on:
  1. hydrogen density: tissues with low hydrogen density (e.g. cortical bone, lung) generate little to no MR signal compared to tissues with high hydrogen density (e.g. water)
  2. magnetic relaxation times (T1 and T2): reflect quantitative alterations in MR signal strength due to intrinsic properties of the tissue and its surrounding chemical and physical environment

<table>
<thead>
<tr>
<th>Table 1. Differences Between Diffusion, T1- and T2-Weighted MR Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Imaging Techniques</strong></td>
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<tr>
<td>Diffusion Weighted Imaging</td>
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<tr>
<td></td>
</tr>
<tr>
<td>T1-Weighted</td>
</tr>
<tr>
<td>T2-Weighted</td>
</tr>
</tbody>
</table>

Positron Emission Tomography Scans

- non-invasive technique that involves exposure to ionizing radiation (~7 mSv)
- nuclear medicine imaging technique that produces images of functional processes in the body
- current generation models integrate PET and CT technologies into a single imaging device (PET-CT) that collects both anatomic and functional information during a single acquisition
- positron-producing radioisotope, such as \(^{18}\)FDG is chemically incorporated into a metabolically active molecule (e.g. glucose), injected into patient, which travels to target organ, accumulates in tissues of interest, and as radioactive substance begins to decay, gamma rays are produced which are detected by PET scanner
- contraindications: pregnancy
- advantages: shows metabolism and physiology of tissues (not only anatomic), in oncology allows diagnosis, staging, restaging, has predictive and prognostic value, can evaluate cardiac viability
- disadvantages: cost, ionizing radiation

Contrast Enhancement

<table>
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<tr>
<th>Table 2. Contrast Agents</th>
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<td><strong>Imaging Modality</strong></td>
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<td>X-Ray/CT</td>
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<td></td>
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<tr>
<td>MRI</td>
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</tbody>
</table>

Methods to Reduce the Risk of Contrast Induced Nephropathy

- Optimal: 0.9% NaCl at 1 ml/kg/hr for 12 hr pre-procedure and 12 hr post-contrast administration
- For same day procedure: 0.9% NaCl or NaHCO\(_3\) at 3 ml/kg/hr for 1-3 hr pre-procedure and for 6 hr post-contrast administration

Contraindications to IV Contrast

- MADD Failure
- Multiple myeloma
- Adverse reaction previously
- DM
- Dehydration
- Failure (renal, severe heart)
Chest X-Ray

Standard Views
- PA: anterior chest against film plate to minimize magnification of the heart size
- lateral: better visualization of retrocardiac space and thoracic spine (more sensitive at picking up pleural effusions)
  - helps localize lesions when combined with PA view
- AP: for bedridden patients (generally a lower quality film than PA because of enlarged cardiac silhouette)
- lateral decubitus: to assess for pleural effusion and pneumothorax in bedridden patients; however, POCUS can also be utilized for both these purposes
- lordotic: angled beam allowing better visualization of apices normally obscured by the clavicles and anterior ribs

Approach to CXR

Basics
- ID: patient name, MRN, sex, age
- date of exam
- markers: right and/or left
- technique: view (e.g. PA, AP, lateral), supine or erect
- indications for the study
- comparison: date of previous study for comparison (if available)
- quality of film: inspiration (6th anterior and 10th posterior ribs should be visible), penetration (thoracic spine should be visible) and rotation (clavicles vs. spinous process)

Analysis
- tubes and lines: check position and be alert for pneumothorax or pneumomediastinum
- soft tissues: neck, axillae, pectoral muscles, breasts/nipples, chest wall
  - nipple markers can help identify nipples (may mimic lung nodules)
  - amount of soft tissue, presence of masses and air (subcutaneous emphysema)
- abdomen (see Abdominal Imaging, MI10)
  - free air under the diaphragm, air-fluid levels, distention in small and large bowels
  - herniation of abdominal contents (i.e. diaphragmatic hernia)
- bones: C-spine, thoracic spine, shoulders, ribs, sternum, clavicles
  - lytic and blastic lesions and fractures
- mediastinum: trachea, heart, great vessels
  - cardiomegaly (cardiothoracic ratio >0.5), tracheal shift, tortuous aorta, widened mediastinum
- hila: pulmonary vessels, mainstem and segmental bronchi, lymph nodes
- lungs: lung parenchyma, pleura, diaphragm
  - comment on abnormal lung opacity, pleural effusions or thickening
  - right hemidiaphragm usually higher than left due to liver
  - right vs. left hemidiaphragm can be discerned on lateral CXR due to heart resting directly on left hemidiaphragm
Anatomy

Localizing Lesions for Parenchymal Lung Disease
- **silhouette sign**: loss of normal interfaces due to lung pathology (consolidation, atelectasis, mass), which can be used to localize disease in specific lung segments; note that pleural or mediastinal disease can also produce the silhouette sign
- **spine sign**: on lateral films, vertebral bodies should appear progressively radiolucent as one moves down the thoracic vertebral column; if they appear more radiopaque, it is an indication of pathology (e.g. consolidation in overlying left lower lobe)
- **air bronchogram**: branching pattern of air filled bronchi on a background of fluid filled airspaces

Table 3. Localization Using the Silhouette Sign

<table>
<thead>
<tr>
<th>Interface Lost</th>
<th>Location of Lung Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVC/right superior mediastinum</td>
<td>RUL</td>
</tr>
<tr>
<td>Right heart border</td>
<td>RML</td>
</tr>
<tr>
<td>Right hemidiaphragm</td>
<td>RLL</td>
</tr>
<tr>
<td>Aortic knob/left superior mediastinum</td>
<td>LUL</td>
</tr>
<tr>
<td>Left heart border</td>
<td>Lingula</td>
</tr>
<tr>
<td>Left hemidiaphragm</td>
<td>LLL</td>
</tr>
</tbody>
</table>

Figure 2. Location of fissures, mediastinal structures, and bony landmarks on CXR

Figure 3. Location of lobes of the lung
Computed Tomography Chest

Approach to CT Chest

- soft tissue window
  - thyroid, chest wall, pleura
  - heart: chambers, coronary artery calcifications, pericardium
  - vessels: aorta, pulmonary artery, smaller vasculature
  - lymph nodes: mediastinal, axillary
- bone window
  - vertebrae, sternum, manubrium, ribs: fractures, lytic lesions, sclerosis
- lung window
  - trachea: patency, secretions
  - bronchial trees: anatomic variants, mucus plugs, airway collapse
  - lung parenchyma: fissures, nodules, fibrosis/interstitial changes
  - pleural space: effusions

Table 4. Types of CT Chest

<table>
<thead>
<tr>
<th>Type</th>
<th>Advantage</th>
<th>Disadvantage</th>
<th>Contrast</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>Scans full lung very quickly (&lt;1 min)</td>
<td>Poor at evaluating diffuse disease</td>
<td>±</td>
<td>Pleural and mediastinal abnormality, Lung cancer staging, Follow up metastases, Empyema vs. abscess</td>
</tr>
<tr>
<td>High Resolution</td>
<td>Thinner slices provide high definition of lung parenchyma</td>
<td>Only 5-10% lung is sampled</td>
<td>No</td>
<td>Hemoptysis, Diffuse lung disease (e.g. sarcoidosis, hypersensitivity pneumonitis, pneumoconiosis), Pulmonary fibrosis, Normal CXR but abnormal PFTs, Characterize solitary pulmonary nodule</td>
</tr>
<tr>
<td>Low Dose</td>
<td>1/5th the radiation</td>
<td>Decreased detail</td>
<td>No</td>
<td>Screening, Follow up infections, lung transplant, metastases</td>
</tr>
<tr>
<td>CTA</td>
<td>Iodinated contrast highlights vasculature</td>
<td>Contrast can cause severe allergic reaction and is nephrotoxic</td>
<td>Yes</td>
<td>PE, Aortic aneurysms, Aortic dissection</td>
</tr>
</tbody>
</table>

Lung Abnormalities

Atelectasis

- pathogenesis: collapse of alveoli due to restricted breathing, blockage of bronchi, external compression, or poor surfactant
- findings
  - increased opacity of involved segment/lobe, vascular crowding, silhouette sign, air bronchograms
  - volume loss: fissure deviation, hilar/mediastinal displacement, diaphragm elevation
  - compensatory hyperinflation of remaining normal lung
- differential diagnosis
  - obstructive (most common): air distal to obstruction is reabsorbed causing alveolar collapse
    - post-surgical, endobronchial lesion, foreign body, inflammation (granulomatous infections, pneumoconiosis, sarcoidosis, radiation injury), or mucous plug (cystic fibrosis)
  - compressive
    - tumour, bulla, effusion, enlarged heart, lymphadenopathy
  - traction (cicatrization): due to scarring, which distorts alveoli and contracts the lung
  - adhesive: due to lack of surfactant
  - hyaline membrane disease, prematurity
  - passive (relaxation): a result of air or fluid in the pleural space
  - pleural effusion, pneumothorax
- management: in the absence of a known etiology, persisting atelectasis must be investigated (i.e. CT thorax) to rule out a bronchogenic carcinoma

Consolidation

- pathogenesis: fluid (water, blood), inflammatory exudates, protein, or tumour in alveoli
- findings
  - air bronchograms: lucent branching bronchi visible through opacification
  - airspace nodules: fluffy, patchy, poorly defined margins with later tendency to coalesce, may take on lobar or segmental distribution
  - silhouette sign

DDx of Airspace Disease

- Pus (e.g. infections such as pneumonia, non-infectious inflammatory process)
- Fluid (e.g. pulmonary edema)
- Blood (e.g. pulmonary hemorrhage)
- Cells (e.g. bronchoalveolar carcinoma, lymphoma)
- Protein (e.g. alveolar proteinosis)
• differential diagnosis
  - fluid: pulmonary edema, blood (trauma, vasculitis, bleeding disorder, pulmonary infarct)
  - inflammatory exudates: bacterial infections, TB, allergic hypersensitivity alveolitis, BOOP, allergic bronchopulmonary aspergillosis, aspiration, sarcoidosis
  - protein: pulmonary alveolar proteinosis
  - tumour: bronchoalveolar carcinoma, lymphoma
• management: varies depending on the pattern of consolidation, which can suggest different etiologies; should also be done in the context of clinical picture

Interstitial Disease
• pathogenesis: pathological process involving the interlobular connective tissue (i.e. “scaffolding of the lung”)
• findings
  - linear: fine lines caused by thickened connective tissue septae
    - Kerley A: long thin lines in upper lobes
    - Kerley B: short horizontal lines extending from lateral lung margin
    - Kerley C: diffuse linear pattern throughout lung
  - seen in pulmonary edema, lymphangitic carcinomatosis, and atypical interstitial pneumonias
  - nodular: 1-5 mm well-defined nodules distributed evenly throughout lung
    - seen in malignancy, pneumoniais and granulomatous disease (e.g. sarcoidosis, miliary TB)
  - reticular (honeycomb): parenchyma replaced by thin-walled cysts suggesting extensive destruction of pulmonary tissue and fibrosis
    - seen in IPF, asbestosis, and CVD
  - watch for pneumothorax as a complication
  - reticulonodular: combination of reticular and nodular patterns
    - may also see signs of airspace disease (atelectasis, consolidation)
• differential diagnosis
  - occupational/environmental exposure
    - inorganic: asbestosis, coal miner’s pneumoconiosis, silicosis, berylliosis, talc pneumoconiosis
    - organic: hypersensitivity pneumonitis, bird fancier’s lung, farmer’s lung (moldy hay), and other organic dust
  - autoimmune: CVD (e.g. rheumatoid arthritis, scleroderma, SLE, polymyositis, mixed connective tissue disease), IB, celiac disease, vasculitis
  - drug-related: antibiotics (cephalosporins, nitrofurantoin), NSAIDs, phenytoin, carbamazepine, fluoxetine, amiodarone, chemotherapy (e.g. methotrexate), heroin, cocaine, methadone
  - infections: non-tuberculous mycobacteria, certain fungal infections
  - idiopathic: hypersensitivity pneumonitis, IPF, BOOP
• for Causes of Interstitial Lung Disease Classified by Distribution, see Respirology, R13
• management: high resolution CT thorax and biopsy

Pulmonary Nodule
• findings: round opacity ± silhouette sign
  - note: do not mistake nipple shadows for nodules; if in doubt, repeat CXR with nipple markers
• differential diagnosis
  - extrapulmonary density: nipple, skin lesion, electrode, pleural mass, bony lesion
  - solitary nodule
    - tumour: carcinoma, hamartoma, metastasis, bronchial adenoma
    - inflammation: histoplasmosis, tuberculosis, coccidioidomycosis
    - vascular: AV fistula, pulmonary varix (dilated pulmonary vein), infarct, embolism
    - multiple nodules: metastases, abscess, granulomatous lung disease (TB, fungal, sarcoid, rheumatoid nodules, silicosis, GPA)
• management: clinical information and CT appearance determine level of suspicion of malignancy
  - if high probability of malignancy, invasive testing (fine needle aspiration, transbronchial/ transthoracic biopsy) is indicated
  - if low probability of malignancy, repeat CXR or CT in 1-3 mo and then every 6 mo for 2 yr; if no change, then >99% chance benign
Table 5. Characteristics of Benign and Malignant Pulmonary Nodules

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Malignant</th>
<th>Benign</th>
</tr>
</thead>
<tbody>
<tr>
<td>Margin</td>
<td>Ill-defined/spiculated (“corona radiata”)</td>
<td>Well-defined</td>
</tr>
<tr>
<td>Contour</td>
<td>Lobulated</td>
<td>Smooth</td>
</tr>
<tr>
<td>Calcification</td>
<td>Eccentric or stippled</td>
<td>Diffuse, central, popcorn, concentric</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>20-480 d</td>
<td>&lt;20 d or &gt;460 d</td>
</tr>
<tr>
<td>Other Features</td>
<td>Cavitation, collapse, adenopathy, pleural effusion, lytic bone lesions, smoking history</td>
<td></td>
</tr>
<tr>
<td>Size</td>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
</tr>
<tr>
<td>Cavitation</td>
<td>Yes, especially with wall thickness &gt;15 mm, eccentric cavity and shaggy internal margins</td>
<td>No</td>
</tr>
<tr>
<td>Satellite Lesions</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Pulmonary Vascular Abnormalities

**Pulmonary Edema**
- pathogenesis: fluid accumulation in the airspaces of the lungs
- findings
  - vascular redistribution/enlargement, cephalization, pleural effusion, cardiomegaly (may be present in cardiogenic edema and fluid overloaded states)
  - fluid initially collects in interstitium
    - loss of definition of pulmonary vasculature
    - peribronchial cuffing
    - Kerley B lines
    - reticulonodular pattern
    - thickening of interlobar fissures
  - as pulmonary edema progresses, fluid begins to collect in alveoli causing diffuse air space disease often in a “bat wing” or “butterfly” pattern in perihilar regions with tendency to spare the outermost lung fields
- differential diagnosis: cardiogenic (e.g. CHF), renal failure, volume overload, non-cardiogenic (e.g. ARDS)

**Pulmonary Embolism**
- pathogenesis: arterial blockage in the lungs due to emboli from pelvic or leg veins, rarely from PICC lines, ports, or air, fat, or amniotic fluid (difficult to diagnose on imaging except by combination of clinical history and CXR and CT findings of ARDS)
- findings
  - CXR: Westermark sign (localized pulmonary oligemia), Hampton’s hump (triangular peripheral infarct), enlarged right ventricle and right atrium, atelectasis, pleural effusion, and rarely pulmonary edema
  - definitive imaging study: CT pulmonary angiography to look for filling defect in contrast-filled pulmonary arteries (emboli can be seen up to 4th order arterial branching)
  - V/Q scan: not a diagnostic study

Pleural Abnormalities

**Pleural Effusion**

Table 6. Sensitivity of Plain Film Views for Pleural Effusion

<table>
<thead>
<tr>
<th>X-Ray Projection</th>
<th>Minimum Volume to Visualize</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lateral decubitus</td>
<td>25 mL: most sensitive</td>
</tr>
<tr>
<td>Upright lateral</td>
<td>50 mL: meniscus seen in the posterior costophrenic sulcus</td>
</tr>
<tr>
<td>PA</td>
<td>200 mL</td>
</tr>
<tr>
<td>Supine</td>
<td>Diffuse haziness</td>
</tr>
</tbody>
</table>

- a horizontal fluid level is seen only in a hydropneumothorax (i.e. both fluid and air within pleural cavity)
- effusion may exert mass effect, shift trachea and mediastinum to opposite side, or cause atelectasis of adjacent lung
- U/S is superior to plain film for detection of small effusions and may also aid in thoracentesis, and POCUS is now standard of care in acute situations
- fluid level >1 cm on lateral decubitus film is indication to perform thoracentesis

**Pneumothorax**
- pathogenesis: gas/air accumulation within the pleural space resulting in separation of the lung from the chest wall
• findings
  ▪ upright chest film allows visualization of visceral pleura as curvilinear line paralleling chest wall, separating partially collapsed lung from pleural air
  ▪ more obvious on expiratory (increased contrast between lung and air) or lateral decubitus films (air collects superiority)
  ▪ more difficult to detect on supine film; look for the “deep (costophrenic) sulcus” sign, “double diaphragm” sign (dome and anterior portions of diaphragm outlined by lung and pleural air, respectively), hyperlucent hemithorax, sharpening of adjacent mediastinal structures
  ▪ mediastinal shift may occur if tension pneumothorax
  ▪ differential diagnosis: spontaneous (tall and thin males, smokers), iatrogenic (lung biopsy, ventilation, CVP line insertion), trauma (associated with rib fractures), emphysema, malignancy, honeycomb lung
  ▪ management: needle decompression or chest tube insertion, repeat CXR to ensure resolution

Asbestos
• asbestos exposure may cause various pleural abnormalities including benign plaques (most common) that may calcify, diffuse pleural fibrosis, effusion, and malignant mesothelioma

Mediastinal Abnormalities

Mediastinal Mass
• the mediastinum is divided into four compartments; this provides an approach to the differential diagnosis of a mediastinal mass
• anterior border formed by the sternum and posterior border by the heart and great vessels
  ▪ 4 Ts: see sidebar
  ▪ cardiophrenic angle mass differential: thymic cyst, epicardial fat pad, foramen of Morgagni hernia
• middle (extending behind anterior mediastinum to a line 1 cm posterior to the anterior border of the thoracic vertebral bodies)
  ▪ esophageal carcinoma, esophageal duplication cyst, metastatic disease, lymphadenopathy (all causes), hiatus hernia, bronchogenic cyst
• posterior (posterior to the middle line described above)
  ▪ neurogenic tumour (e.g. neurofibroma, schwannoma), multiple myeloma, pheochromocytoma, neurenteric cyst, thoracic duct cyst, lateral meningocele, Bochdalek hernia, extramedullary hematomas
• superior boundaries (superiorly by thoracic inlet, inferiorly by plane of the sternal angle, anteriorly by manubrium, posteriorly by T1-T4, laterally by pleura)
• in addition, any compartment may give rise to lymphoma, lung cancer, aortic aneurysm or other vascular abnormalities, abscess, and hematoma

Enlarged Cardiac Silhouette
• heart borders
  ▪ on PA view, right heart border is formed by right atrium; left heart border is formed by left atrium and left ventricle
  ▪ on lateral view, anterior heart border is formed by right ventricle; posterior border is formed by left atrium (superior to left ventricle) and left ventricle
• cardiothoracic ratio = greatest transverse dimension of the central shadow relative to the greatest transverse dimension of the thoracic cavity
  ▪ using a good quality erect PA chest film in adults, cardiothoracic ratio of >0.5 is abnormal
  ▪ differential of ratio >0.5
    ▪ cardiomegaly (myocardial dilatation or hypertrophy)
    ▪ pericardial effusion
    ▪ poor inspiratory effort/low lung volumes
    ▪ pectus excavatum
  ▪ ratio <0.5 does not exclude enlargement (e.g. cardiomegaly + concomitant hyperinflation)
• pericardial effusion: globular heart with loss of indentations on left mediastinal border
• RA enlargement: increase in curvature of right heart border and enlargement of SVC
• LA enlargement: straightening of left heart border; increased opacity of lower right side of cardiovascular shadow (double heart border); elevation of left main bronchus (specifically, the upper lobe bronchus on the lateral film), distance between left main bronchus and “double” heart border >7 cm, splayed carina (late sign)
• RV enlargement: elevation of cardiac apex from diaphragm; anterior enlargement leading to loss of retrosternal air space on lateral; increased contact of right ventricle against sternum
• LV enlargement: displacement of cardiac apex inferiorly and posteriorly – “boot-shaped” heart
### Tubes, Lines, and Catheters

- Ensure appropriate placement and assess potential complications of lines and tubes
- Avoid mistaking a line/tube for pathology (e.g., oxygen rebreather mask for pneumothoraces)

#### Central Venous Catheter
- Used for fluid and medication administration, vascular access for hemodialysis, and CVP monitoring
- Tip must be located proximal to right atrium to prevent inducing arrhythmias or perforating wall of atrium
  - If monitoring CVP, catheter tip must be proximal to venous valves
- Tip of well-positioned central venous catheter projects over silhouette of SVC in a zone demarcated superiorly by the anterior first rib end and clavicle, and inferiorly by top of RA
- Course should parallel course of SVC – if appears to bend as it approaches wall of SVC or appears perpendicular, catheter may damage and ultimately perforate wall of SVC
- Complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

#### Endotracheal Tube
- Frontal chest film: tube projects over trachea and shallow oblique or lateral chest radiograph will help determine position in 3 dimensions
- Progressive gaseous distention of stomach on repeat imaging is concerning for esophageal intubation
- Tip should be located 4 cm above tracheal carina – avoids bronchus intubation and vocal cord irritation
- Maximum inflation diameter <3 cm to avoid necrosis of tracheal mucosa and rupture – ensure diameter of balloon is less than tracheal diameter above and below balloon
- Complications: aspiration (parenchymal opacities), pharyngeal perforation (subcutaneous emphysema, pneumomediastinum, mediastinitis)

#### Nasogastric Tube
- Tip and sideport should be positioned distal to esophagogastric junction and proximal to gastric pylorus
- Radiographic confirmation of tube is mandatory because clinical techniques for assessing tip position may be unreliable
- Complications: aspiration (parenchymal opacities), intracranial perforation (trauma patients), pneumothorax

#### Swan-Ganz Catheter
- To monitor pulmonary capillary wedge pressure and to measure cardiac output for suspected LV dysfunction
- Tip should be positioned within right or left main pulmonary arteries or in one of their large, lobar branches
- If tip is located more distally, increased risk of prolonged pulmonary artery occlusion resulting in pulmonary infarction or, rarely, pulmonary artery rupture
- Complications: pneumothorax, bleeding (mediastinal, pleural), air embolism

#### Chest Tube
- In dorsal and caudal portion of pleural space to evacuate fluid
- In ventral and cephalad portions of pleural space to evacuate pneumothoraces
- Tube may lie in fissure as long as functioning
- Complications: lung perforation (mediastinal opacities)

### Abdominal Imaging

#### Abdominal X-Ray
- AXR 3 most common views: left lateral decubitus, supine, erect upright (see Figure 16)
- Indications
  - Acute abdomen: bowel perforation, toxic megacolon, bowel ischemia, small bowel obstruction, large bowel obstruction
  - Chronic symptoms: constipation, calcifications (gallstones, renal stones, urinary bladder stones, etc.)
  - Not useful in: GI bleeds, chronic anemia, vague GI symptoms
Anatomy

- abdomen divided into 2 cavities
  - peritoneal cavity: lined by peritoneum that wraps around most of the bowel, the spleen, and most of the liver; forms a recess lateral to both the ascending and descending colon (paracolic gutters)
  - retroperitoneal cavity: contains several organs situated posterior to the peritoneal cavity; the contour of these can often be seen on radiographs

Table 7. Differentiating Small and Large Bowel

<table>
<thead>
<tr>
<th>Property</th>
<th>Small Bowel</th>
<th>Large Bowel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mucosal Folds</td>
<td>Uninterrupted valvulae conniventes (or plicae</td>
<td>Interrupted haustra extend only partway across</td>
</tr>
<tr>
<td></td>
<td>circularis)</td>
<td>lumen</td>
</tr>
<tr>
<td>Location</td>
<td>Central</td>
<td>Peripheral (picture frame)</td>
</tr>
<tr>
<td>Maximum Diameter</td>
<td>3 cm</td>
<td>6 cm (9 cm at cecum)</td>
</tr>
<tr>
<td>Maximum Fold Thickness</td>
<td>3 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Other</td>
<td>Rarely contains solid fecal material</td>
<td>Commonly contains solid fecal material</td>
</tr>
</tbody>
</table>

Approach to Abdominal X-Ray

- mnemonic: “Free ABDO”
- “Free”: free air and fluid
  - free fluid
    - small amounts of fluid: increased distance between lateral fat stripes and adjacent colon may indicate free peritoneal fluid in the paracolic gutters
    - large amounts of fluid: diffuse increased opacification on supine film; bowel floats to centre of anterior abdominal wall
    - ascites and blood (hemoperitoneum) are the same density on the radiograph and therefore cannot be differentiated
    - free intraperitoneal air suggests rupture of a hollow viscus (anterior duodenum, transverse colon), penetrating trauma, or recent (<7 d) surgery
  - “A”: air in the bowel (can be normal, ileus, or obstruction)
    - volvulus – twisting of the bowel upon itself; from most to least common:
      - sigmoid: “coffee bean” sign (massively dilated sigmoid projects to right or mid-upper abdomen) with proximal dilation
      - cecal: massively dilated bowel loop projecting to left or mid-upper abdomen with small bowel dilation
      - gastric: rare
      - transverse colon: rare (usually young individuals)
      - small bowel: “corkscrew sign” (rarely diagnosed on plain films, seen best on CT)
    - toxic megacolon
      - manifestation of fulminant colitis
      - extreme dilatation of colon (>6.5 cm) with mucosal changes (e.g. foci of edema, ulceration, pseudopolyps), loss of normal haustral pattern
  - “B”: bowel wall thickening
    - increased soft tissue density in bowel wall, thumb-like indentations in bowel wall ("thumb-printing"), or a picket-fence appearance of the valvulae conniventes ("stacked coin" appearance)
    - may be seen in IBD, infection, ischemia, hypoproteinemic states, and submucosal hemorrhage
  - “D”: densities
    - bones: look for gross abnormalities of lower ribs, vertebral column, and bony pelvis
    - abnormal calcifications: approach by location
      - RUQ: renal stone, adrenal calcification, gallstone, porcelain gallbladder
      - RLQ: ureteral stone, appendicolith, gallstone ileus
      - LUQ: renal stone, adrenal calcification, tail of pancreas
      - LLQ: ureteral stone
      - central: aorta/aortic aneurysm, pancreas, lymph nodes
      - pelvis: phleboliths (i.e. calcified veins), uterine fibroids, bladder stones
  - “O”: organs
    - kidney, liver, gallbladder, spleen, pancreas, urinary bladder, psoas shadow
    - outlines can occasionally be identified because they are surrounded by more lucent fat, but all are best visualized with other imaging modalities (CT, MRI)
Table 8. Abnormal Air on Abdominal X-Ray

<table>
<thead>
<tr>
<th>Air</th>
<th>Appearance</th>
<th>Common Etiologies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extraluminal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraperitoneal</td>
<td>Upright film: air under diaphragm</td>
<td>Perforated viscus</td>
</tr>
<tr>
<td>(pneumoperitoneum)</td>
<td>Left lateral decubitus film: air between liver and abdominal wall</td>
<td>Post-operative (up to 10 d to be resorbed)</td>
</tr>
<tr>
<td>Supine film: gas outlines of structures not normally seen:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Inner and outer bowel wall (Rigler’s sign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Falciform ligament</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Peritoneal cavity (“football” sign)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retropertoneal</td>
<td>Gas outlining retropertoneal structures allowing increased visualization:</td>
<td>Perforation of retropertoneal segments of bowel:</td>
</tr>
<tr>
<td></td>
<td>• Psoas shadows</td>
<td>duodenal ulcer, post-colonoscopy</td>
</tr>
<tr>
<td></td>
<td>• Renal shadows</td>
<td></td>
</tr>
<tr>
<td>Intramural</td>
<td>Lucent air streaks in bowel wall, 2 types:</td>
<td>1. Linear: ischemia, necrotizing enterocolitis</td>
</tr>
<tr>
<td>(pneumatosis intestinalis)</td>
<td>1. Linear</td>
<td>2. Rounded/cystoides (generally benign): primary (idiopathic), secondary to COPD</td>
</tr>
<tr>
<td></td>
<td>2. Rounded (cystoides type)</td>
<td></td>
</tr>
<tr>
<td>Intraluminal</td>
<td>Dilated loops of bowel, air-fluid levels</td>
<td>Adynamic (paralytic) ileus, mechanical bowel obstruction</td>
</tr>
<tr>
<td>Loculated</td>
<td>Mottled, localized in abnormal position without normal bowel features</td>
<td>Abscess (evaluate with CT)</td>
</tr>
<tr>
<td>Biliary</td>
<td>Air centrally over liver</td>
<td>Sphincterotomy, gallstone ileus, erosive peptic ulcer, cholangitis, emphysematous cholecystitis</td>
</tr>
<tr>
<td>Portal Venous</td>
<td>Air peripherally over liver in branching pattern</td>
<td>Bowel ischemia/infarction</td>
</tr>
</tbody>
</table>

Table 9. Adynamic Ileus vs. Mechanical Obstruction

<table>
<thead>
<tr>
<th>Feature</th>
<th>Adynamic Ileus</th>
<th>Mechanical Obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calibre of Bowel Loops</td>
<td>Normal or dilated</td>
<td>Usually dilated</td>
</tr>
<tr>
<td>Air-Fluid Levels (erect and left lateral decubitus films only)</td>
<td>Same level in the same single loop</td>
<td>Multiple air fluid levels giving “step ladder” appearance, dynamic (indicating peristalsis present), “string of pearls” (row of small gas accumulations in the dilated valvulae conniventes)</td>
</tr>
<tr>
<td>Distribution of Bowel Gas</td>
<td>Air throughout GI tract is generalized or localized</td>
<td>Dilated bowel up to the point of obstruction (i.e. transition point)</td>
</tr>
<tr>
<td></td>
<td>• In a localized ileus (e.g. pancreatitis, appendicitis), dilated “sentinel loop” remains in the same location on serial films, usually adjacent to the area of inflammation</td>
<td>No air distal to obstructed segment</td>
</tr>
</tbody>
</table>

Abdominal CT

- indications for plain CT: renal colic, hemorrhage
- indications for CT with contrast
  - IV contrast given immediately before or during CT to allow identification of arteries and veins
  - portal venous phase: indicated for majority of cases
  - biphasic (arterial and portal venous phases): liver, pancreas, bile duct tumours
  - caution: contrast allergy (may premedicate with steroids and antihistamine)
  - contraindication: impaired renal function, based on eGFR
  - oral contrast: barium or water soluble (water soluble if suspected perforation) given in most cases to demarcate GI tract
  - rectal contrast: given for investigation of colonic lesions

Biliary vs. Portal Venous Air

“Go with the flow”: air follows the flow of bile or portal venous blood
Biliary air is most prominent centrally over the liver
Portal venous air is most prominent peripherally

Figure 16. Normal AXRs: (left) supine anteroposterior AXR, (middle) upright anteroposterior AXR, and (right) left lateral decubitus AXR
Approach to Abdominal Computed Tomography

- look through all images in gestalt fashion to identify any obvious abnormalities
- look at each organ/structure individually, from top to bottom evaluating size and shape of each area of increased or decreased density
- evaluate the following
  - soft tissue window
  - liver, gallbladder, spleen, and pancreas
  - adrenals, kidneys, ureters, and bladder
  - stomach, duodenum, small bowel mesentery, and colon/appendix
  - retroperitoneum: aorta, vena cava, and mesenteric vessels; look for adenopathy in vicinity of vessels
  - peritoneal cavity for fluid or masses
  - abdominal wall and adjacent soft tissue
  - lung window
  - visible lung (bases)
  - bone window
  - vertebrae, spinal cord, and bony pelvis

CT and Bowel Obstruction

- cause of bowel obstruction rarely found on plain films – CT is best choice for imaging
- the “3,6,9” rule is a very useful guide to determining when the bowel is dilated; the maximum diameter of the bowel is 3 cm for small bowel, 6 cm for large bowel, and 9 cm for cecum; this can also be useful to distinguish small and large bowel, and to assess for ‘impending’ cecal perforation (e.g. post-untreated Ogilvie’s syndrome)
- closed-loop obstruction: an obstruction in two locations (usually small bowel) creating a loop of bowel segment obstructed both proximally and distally; complications (e.g. ischemia, perforation, necrosis) may occur quickly

CT Colonography (virtual colonoscopy)

- emerging imaging technique for evaluation of intraluminal colonic masses (i.e. polyps, tumours)
- two CT scans of the abdomen (prone and supine) after the instillation of carbon dioxide into a prepped colon
- computer reconstruction of 2D CT images into a 3D intraluminal view of the colon
- lesions seen on 3D images correlated with 2D axial images
- indications: surveillance in low-risk patients, incomplete colonoscopy, staging of obstructing colonic lesions

Contrast Studies

Table 10. Types of Contrast Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Organ</th>
<th>Procedure Description</th>
<th>Assessment</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cine Esophagram</td>
<td>Cervical esophagus</td>
<td>Contrast agent swallowed recorded for later playback and analysis</td>
<td>Dysphagia, swallowing incoordination, recurrent aspiration, post-operative cleft palate repair</td>
<td>Aspiration, webs (partial occlusion), Zenker’s diverticulum, cricopharyngeal bar, laryngeal tumour</td>
</tr>
<tr>
<td>Barium Swallow</td>
<td>Thoracic esophagus</td>
<td>Contrast agent swallowed under fluoroscopy, selective images captured</td>
<td>Dysphagia, rule out GERD, post esophageal surgery</td>
<td>Achalasia, hiatus hernia, esophagitis, cancer, esophageal tear</td>
</tr>
<tr>
<td>Upper GI Series</td>
<td>Thoracic esophagus, stomach, or duodenum</td>
<td>Double contrast study: 1. Barium to coat mucosa, then 2. Gas pills for distention Patient NPO after midnight</td>
<td>Dyspepsia, investigate possible upper GI bleed, weight loss/anemia, post gastric surgery</td>
<td>Ulcers, neoplasms, filling defects</td>
</tr>
<tr>
<td>Barium Enema</td>
<td>Large bowel Rectum may be obscured by tube – therefore must do sigmoidoscopy to exclude rectal lesions Colon filled retrograde with barium and air or CO₂ Bowel prep the night before procedure</td>
<td>Altered bowel habits, suspected lower GI bleed, weight loss/anemia, rule out large bowel obstruction, suspected perforation, check surgical anastomosis, history of polype</td>
<td>Diverticulosis, neoplasms, IBD, intussusception (can be reduced with barium or air enema), volvulus</td>
<td></td>
</tr>
<tr>
<td>Small Bowel Follow Through</td>
<td>Entire small bowel</td>
<td>Single contrast images following upper GI series</td>
<td>GI bleed with non-diagnostic upper GI series/barium enema, weight</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
</tr>
<tr>
<td>Enteroclysis (MRI or CT)</td>
<td>Entire small bowel Enteroclysis: patient drinks 1-2 L of sorbitol, psyllium, or barium solution to distend small bowel Enteroclysis: NJ tube used to pump barium, psyllium, or sorbitol contrast media directly into small bowel</td>
<td>IBD, malabsorption, weight loss/anemia, Meckel’s diverticulum</td>
<td>Neoplasms, IBD, malabsorption, infection</td>
<td></td>
</tr>
</tbody>
</table>
Specific Visceral Organ Imaging

Liver
- U/S: assessment of cysts, abscesses, tumours, biliary tree
- CT ± IV: most popular procedure for imaging the liver parenchyma (primary liver tumours, metastases, cysts, abscesses, trauma, cirrhosis)
- MR: also excellent in evaluation of primary liver tumours, liver metastases, and other parenchymal conditions, and is particularly helpful in differentiating common benign hepatic hemangiomas from primary liver tumours and metastases
- Elastography: measures shear wave velocity by U/S (Fibroscan) or MRI (MR elastography) to non-invasively quantify liver fibrosis
- findings
  - advanced cirrhosis: liver small and irregular (fibrous scarring, segmental atrophy, regenerating nodules)
  - portal HTN: increased portal vein diameter, collateral veins, splenomegaly (≥12 cm), portal vein thrombosis, recanalization of the umbilical vein
  - porto-systemic shunts: caput medusa, esophageal varices, spontaneous spleno-renal shunt
  - U/S: cirrhosis appears nodular and hyperechoic with irregular areas of atrophy of the right lobe and hypertrophy of the caudate or left lobes
  - CT: fatty infiltration appears hypodense
- in order to be visualized, some masses require contrast

Table 11. Triphasic/Quadriphasic Liver Protocol

<table>
<thead>
<tr>
<th>Phase</th>
<th>Time Frame</th>
<th>Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Contrast CT</td>
<td>0</td>
<td>For all initial investigations of liver lesions</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post radiofrequency ablation of liver tumours</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not usually indicated for surveillance imaging</td>
</tr>
<tr>
<td>Arterial Phase</td>
<td>20-30 s</td>
<td>Early and late arterial phase on multidetector CT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Late arterial phase best for discriminating hypervascular HCC</td>
</tr>
<tr>
<td>Portal Venous Phase</td>
<td>60-70 s</td>
<td>Provides maximum enhancement of hepatic tissue</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Most tumours supplied by hepatic artery are relatively hypovascular, therefore appear as low-attenuation masses in portal venous phase</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypervascular tumours wash out (HCC)</td>
</tr>
<tr>
<td>Equilibrium (Delayed) Phase</td>
<td>120-180 s</td>
<td>Hemangioma: persistent enhancement suggests blood</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Enhancement of fibrous/scar tissue (HCC capsule, focal nodular hyperplasia, cholangiocarcinoma)</td>
</tr>
</tbody>
</table>

Table 12. Imaging of Liver Masses

<table>
<thead>
<tr>
<th>Mass</th>
<th>U/S</th>
<th>CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastases</td>
<td>Multiple masses of variable echotexture</td>
<td>Usually low attenuation on contrast enhanced scan</td>
</tr>
<tr>
<td>HCC</td>
<td>Single/multiple masses, or diffuse infiltration</td>
<td>Hypervascular enhances in arterial and washes out in venous phase with portal venous tumour thrombus</td>
</tr>
<tr>
<td>Abscess</td>
<td>Poorly defined, irregular margin, hypoechogenic contents</td>
<td>Low-attenuation lesion with an irregular enhancing wall</td>
</tr>
<tr>
<td>Hydatid Cyst</td>
<td>Simple/multiloculated cyst</td>
<td>Low-attenuation simple or multiloculated cyst; calcification</td>
</tr>
<tr>
<td>Hemangioma</td>
<td>Homogeneous hyperechoic mass</td>
<td>Peripheral globular enhancement in arterial phase scans; central-filling and persistent enhancement on delayed scans</td>
</tr>
<tr>
<td>Focal Nodular</td>
<td>Well-defined mass, central scar seen in 50%</td>
<td>Hypervascular mass in arterial phase and isodensity attenuation to liver in portal venous phase</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td>Most common in young women taking oral contraceptives. Well-defined mass with hyperechoic areas due to hemorrhage</td>
<td>Well-defined hypervascular lesion with enlarged central vessel becoming slightly isodense in venous phase</td>
</tr>
<tr>
<td>Adenoma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Spleen
- U/S, CT: nuclear medicine scan (nuclear medicine only to distinguish ectopic splenic tissue from enhancing tumours)
- CT for splenic trauma (hemorrhage)

Pancreas
- tumours
  - U/S: mass is more echogenic than normal pancreatic tissue
  - CT: preferred modality for diagnosis/staging
  - ductal dilation secondary to stone/tumour
  - MRCP: imaging of ductal system using MRI cholangiography; no therapeutic potential
ERCP: endoscope to inject dye into the biliary tree and x-ray imaging to assess pancreatic and biliary ducts; therapeutic potential (stent placement, stone retrieval); acute pancreatitis is a complication in 5% of diagnostic procedures and 10% of therapeutic procedures.

**Biliary Tree**
- U/S: bile ducts usually visualized only if dilated, secondary to obstruction (e.g. cholelithiasis, benign stricture, mass)
- CT: dilated intrahepatic ductules seen as branching, tubular structures following pathway of portal venous system
- MRCP, ERCP, PTC: further evaluation of obstruction and possible intervention

### “itis” Imaging

**Acute Cholecystitis**
- pathogenesis: inflammation of gallbladder resulting from sustained gallstone impaction in cystic duct or, in the case of acalculous cholecystitis, due to gallbladder ischemia or cholestasis (see General Surgery, GS46)
- best imaging modality: U/S (best sensitivity and specificity); nuclear medicine (HIDA scan) can help diagnose cases of acalculous or chronic cholecystitis
- findings: thick wall, pericholecystic fluid, gallstones, dilated gallbladder, positive sonographic Murphy's sign
- management: cholecystectomy

**Acute Appendicitis**
- pathogenesis: luminal obstruction → bacterial overgrowth → inflammation/swelling → increased pressure → localized ischemia → gangrene/perforation → localized abscess or peritonitis (see General Surgery, GS28)
- best imaging modality: U/S or CT
- findings
  - U/S: thick-walled appendix, appendicolith, dilated fluid-filled appendix, non-compressible; may also demonstrate other causes of RLQ pain (e.g. ovarian abscess, IBD, ectopic pregnancy)
  - CT: enlargement of appendix (>6 mm in outer diameter), enhancement of appendiceal wall, adjacent inflammatory stranding, appendicolith; also facilitates percutaneous abscess drainage
- management: appendectomy

**Acute Diverticulitis**
- pathogenesis: erosion of the intestinal wall (most commonly rectosigmoid) by increased intraluminal pressure or inspissated food particles → inflammation and focal necrosis → micro- or macroscopic perforation (see General Surgery, GS31)
- best imaging modality: CT is modality of choice, although U/S is sometimes used
- contrast: oral and rectal contrast given before CT to opacify bowel
- findings
  - cardinal signs: thickened wall, mesenteric infiltration, gas-filled diverticula, abscess
  - CT can be used for percutaneous abscess drainage before or in lieu of surgical intervention
  - sometimes difficult to distinguish from perforated cancer (therefore send abscess fluid for cytology and follow up with colonoscopy)
  - if chronic, may see fistula (most common to bladder) or sinus tract (linear or branching structures)
- management: ranges from antibiotic treatment to surgical intervention; can use imaging to follow progression

**Acute Pancreatitis**
- pathogenesis: activation of proteolytic enzymes within pancreatic cells leading to local and systemic inflammatory response (see Gastroenterology, G45); a clinical/biochemical diagnosis
- best imaging modality: imaging used to support diagnosis and evaluate for complications (diagnosis cannot be excluded by imaging alone)
  - U/S good for screening and follow-up
  - CT is useful in advanced stages and in assessing for complications (1st line imaging test)
- findings
  - U/S: hypoechoic enlarged pancreas (if ileus present, gas obscures pancreas)
  - CT: enlarged pancreas, edema, stranding changes in surrounding fat with indistinct fat planes, mesenteric and Gerota’s fascia thickening, pseudocyst in lesser sac, abscess (gas or thick-walled fluid collection), pancreatic necrosis (low attenuation gas-containing non-enhancing pancreatic tissue), hemorrhage
- management: supportive therapy
  - CT-guided needle aspiration and/or drainage done for abscess when clinically indicated
  - pseudocyst may be followed by CT and drained if symptomatic
Chronic Pancreatitis
- pathogenesis: (see Gastroenterology, G45)
- best imaging modality: MRCP (can show calcification and duct obstruction)
- findings: U/S, CT scan, and MRI may show calcifications, ductal dilatation, enlargement of the pancreas and fluid collections (e.g. pseudocysts) adjacent to the gland

Angiography of Gastrointestinal Tract
- anatomy of the GI tract arterial blood supply branches
  - celiac artery: hepatic, splenic, gastroduodenal, left/right gastric
  - superior mesenteric artery: jejunal, ileal, ileo-colic, right colic, middle colic
  - inferior mesenteric artery: left colic, superior rectal
- imaging modalities
  - conventional angiogram: invasive (usual approach via femoral puncture), catheter used
    - flush aortography: catheter injection into abdominal aorta, followed by selective arteriography of individual vessels
  - CT angiogram: modality of choice, non-invasive using IV contrast (no catheterization required)

Genitourinary System and Adrenal

Urological Imaging
KUB (Kidney, Ureter, and Bladder X-ray)
- a frontal supine radiograph of the abdomen
- indication: useful in evaluation of radio-opaque renal stones (all stones but uric acid and indinavir), indwelling ureteric stents /catheters, and foreign bodies in abdomen
- findings: addition of IV contrast excreted by the kidney (intravenous urogram) allows greater visualization of the urinary tract, but has been largely replaced by CT urography

Abdominal CT
Renal Masses
- Bozniak classification for cystic renal masses
- class I-II: benign and can be disregarded
- class IIF: should be followed
- class III-IV: suspicious for malignancy, requiring additional workup

Table 13. Bozniak Classification for Cystic Renal Masses

<table>
<thead>
<tr>
<th>Classes</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simple Renal Cysts</td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>Fluid-attenuating well-defined lesion, no septation, no calcification, no solid components, hair thin wall</td>
</tr>
<tr>
<td>Class II</td>
<td>Same as class I + fine calcification or moderately thickened calcification in septae or walls; also includes hyperdense cysts (&lt;3 cm) that do not enhance with contrast</td>
</tr>
<tr>
<td>Complex Renal Cysts</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>Thick irregular walls ± calcifications ± septated, enhancing walls or septa with contrast</td>
</tr>
<tr>
<td>Renal Cell Carcinoma</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>Same as class III + soft tissue enhancement with contrast (defined as &gt;10 Hounsfield unit increase, characterizing vascularity) with de-enhancement in venous phase ± areas of necrosis</td>
</tr>
</tbody>
</table>

- plain CT KUB indications: general imaging of renal anatomy, renal colic symptoms, assessment of renal calculi (size and location), and hydropnephrosis prior to urological treatment
- CT urography indications: investigation of cause of microscopic/gross hematuria, detailed assessment of urinary tracts (excretory phase), high sensitivity (95%) for uroepithelial malignancies of the upper urinary tracts, assessment of renal calculi
  - phases: unenhanced, excretory
- renal triphasic CT indications: standard imaging for renal masses, allows accurate assessment of renal arteries and veins, better characterization of suspicious renal masses, especially in differentiating renal cell carcinoma from more benign masses, and pre-operative staging
  - phases: unenhanced, arterial and venous (nephrographic), excretory

Figure 21. Triphasic CT of an angiomyolipoma: showing fat density with non-contrast scan, mildly enhancing with contrast

Angiography requires active blood loss 1-1.5 mL/min under optimal conditions for a bleeding site to be visualized in cases of lower GI bleeding

Imaging Modality Based on Presentation
- Acute testicular pain = Doppler, U/S
- Amenorrhea = U/S, MRI (brain)
- Bloody urine = U/S, CT
- Flank pain = U/S, CT
- Hematuria = U/S, Cystoscopy, CT
- Infertility = HSG, MRI
- Lower abdominal mass = U/S, CT
- Lower abdominal pain = U/S, CT
- Renal colic = U/S, KUB, CT
- Testicular mass = U/S
- Urethral stricture = Urethrogram
Ultrasound
- **indications**: initial study for evaluation of kidney size and nature of renal masses (solid vs. cystic renal masses vs. complicated cysts); technique of choice for screening patients with suspected hydronephrosis (no IV contrast injection, no radiation to patient, and can be used in patients with renal failure); TRUS useful to evaluate prostate gland and guide biopsies; Doppler U/S to assess renal vasculature
- **findings**: solid renal masses are echogenic (bright on U/S), cystic renal masses have smooth well-defined walls with anechoic interior (dark on U/S), and complicated cysts have internal echoes within a thickened, irregular wall

Retrograde Pyelography
- **indications**: visualize the urinary collecting system via a cystoscope, ureteral catheterization, and retrograde injection of contrast medium, visualized by radiograph or fluoroscopy; ordered when the intrarenal collecting system and ureters cannot be opacified using intravenous techniques (patient with impaired renal function, high grade obstruction)
- **findings**: only yields information about the collecting systems (renal pelvis and associated structures), no information regarding the parenchyma of the kidney

Voiding Cystourethrogram
- bladder filled with contrast to the point where voiding is triggered
- fluoroscopy (continuous, real-time) to visualize bladder
- **indications**: children with recurrent UTIs, hydronephrosis, hydroureter, suspected lower urinary tract obstruction or vesicoureteral reflux
- **findings**: contractility and evidence of vesicoureteric reflux

Retrograde Urethrogram
- a small Foley catheter placed into penile urethral opening
- **indications**: used mainly to study strictures or trauma to the male urethra; first-line study if trauma with blood present at urethral meatus

MRI
- **advantages**: high spatial and tissue resolution, lack of exposure to ionizing radiation and nephrotoxic contrast agents
- **indications**: indicated over CT for depiction of renal masses in patients with previous nephron sparing surgery, patients requiring serial follow-up (less radiation dosage), patients with reduced renal function, patients with solitary kidneys, clinical staging of prostate cancer (endorectal coil MRI)

Renal Nuclear Scan

<table>
<thead>
<tr>
<th>Type of Test</th>
<th>Uses</th>
<th>Radionuclide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renogram</td>
<td>assess renal function and collecting system: evaluation of renal failure, workup of urinary tract obstruction and renovascular HTN, investigation of renal transplant</td>
<td>IV (^{99m})Tc-pentetate (DTPA) or meriactide (MAG3), and imaged at 1-3 s intervals with a gamma camera over the first 60 s to assess perfusion</td>
</tr>
<tr>
<td>Morphological</td>
<td>Assess renal anatomy: investigation of pyelonephritis and cortical scars</td>
<td>(^{99m})Tc-DMSA, (^{99m})Tc-glucopentonate</td>
</tr>
</tbody>
</table>

Gynecological Imaging

Ultrasound
- transabdominal and transvaginal are the primary modalities, and are indicated for different scenarios
- transabdominal requires a full bladder to push out air containing loops of bowel
  - **indications**: good initial investigation for suspected pelvic pathology
- TVUS provides enhanced detail of deeper/smaller structures by allowing use of higher frequency sound waves at reduced distances
  - **indication**: improved assessment of ovaries, first trimester development, and ectopic pregnancies

Hysterosalpingogram
- performed by x-ray images of the pelvis after cannulation of the cervix and subsequent injection of opacifying agent
- **indications**: useful for assessing pathology of the uterine cavity and fallopian tubes, evaluating uterine abnormalities (e.g. bicornuate uterus), or evaluation of fertility (absence of flow from tubes to peritoneal cavity indicates obstruction)

CT/MRI
- **indications**: evaluating pelvic structures, especially those adjacent to the adnexa and uterus
- invaluable for staging gynecological malignancies and detecting recurrence

Figure 22. Triphasic CT of a renal cell carcinoma: showing arterial enhancing right renal lesion with venous washout (shunting)

Figure 23. Retrograde urethrogram: demonstrating stricture in the membranous urethra

Figure 24. Transabdominal U/S: pregnancy, 18 wk fetus

Figure 25. Hysterosalpingogram: left hydrosalpinx

Pregnancy should always be ruled out by \(\beta\)-hCG before CT of a female pelvis (or any organ system) is performed
Sonohysterogram
- saline infusion sonohysterogram involves instilling fluid into the uterine cavity transcervically to provide enhanced endometrial visualization during TVUS examination
- indications: abnormal uterine bleeding, uterine cavity abnormalities that are suspected or noted on TVUS (e.g. leiomyomas, polyps, synechiae), congenital abnormalities of the uterine cavity, infertility, recurrent pregnancy loss
- contraindications: pregnancy, pelvic infection

Table 15. Typical and Atypical Findings on a Sonohysterogram

<table>
<thead>
<tr>
<th>Finding</th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polyps</td>
<td>A well-defined, homogeneous, polypoid lesion isoechoic to the endometrium with preservation of the endometrium-myometrial interface</td>
<td>Atypical features include cystic components, multiple polyps, broad base, hypeoecogenicity or heterogeneity</td>
</tr>
<tr>
<td>Leiomyoma</td>
<td>Well-defined, broad-based, hypeoecogenic, solid masses with shadowing. Overlying layer of endometrium is echogenic and distorts the endometrium-myometrial interface</td>
<td>Pedunculation or multilobulated surface</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>Diffuse echogenic endometrial thickening without focal abnormality, although focal lesions can occur. Endometrial cancer is typically a diffuse process, but early cases can be focal and appear as a polypoid mass</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adhesions</td>
<td>Mobile, thin, echogenic bands that cut across the endometrial cavity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Thick, broad-based bands that can completely obliterate the endometrial cavity, as in Asherman’s syndrome</td>
<td></td>
</tr>
</tbody>
</table>

Adrenal Mass
- imaging modality: most often identified on CT scan as ‘incidentaloma,’ can also use CT/MRI to distinguish benign from malignant masses

Table 16. Adrenal Mass Findings on CT and MRI

<table>
<thead>
<tr>
<th>Factors</th>
<th>Adrenocortical Adenoma</th>
<th>Adrenocortical Carcinoma</th>
<th>Pheochromocytoma</th>
<th>Metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter (CT)</td>
<td>Usually ≤3 cm</td>
<td>Usually &gt;4 cm</td>
<td>Usually &gt;3 cm</td>
<td>Variable around &lt;3 cm</td>
</tr>
<tr>
<td>Shape (CT)</td>
<td>Smooth margins and round/oval</td>
<td>Irregular with unclear margins</td>
<td>Round/oval with clear margins</td>
<td>Oval/irregular with unclear margins</td>
</tr>
<tr>
<td>Texture (CT)</td>
<td>Homogeneous</td>
<td>Heterogeneous with mixed densities</td>
<td>Heterogeneous with cystic areas</td>
<td>Heterogeneous with mixed densities</td>
</tr>
<tr>
<td>Vascularity (CT)</td>
<td>Not highly vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
<td>Usually vascular</td>
</tr>
<tr>
<td>Washout of Contrast Medium on CT</td>
<td>≥50% at 10 min</td>
<td>&lt;50% at 10 min</td>
<td>&lt;50% at 10 min</td>
<td>&lt;50% at 10 min</td>
</tr>
<tr>
<td>Growth</td>
<td>Stable or very slow (&lt;1 cm/yr)</td>
<td>Usually rapid (&gt;2 cm/yr)</td>
<td>Slow (0.5-1 cm/yr)</td>
<td>Variable</td>
</tr>
<tr>
<td>Other Findings</td>
<td>Usually low density due to intracellular fat</td>
<td>Necrosis, calcifications, and hemorrhage</td>
<td>Hemorrhage</td>
<td>Occasionally hemorrhage</td>
</tr>
<tr>
<td>MRI on T2 Weighted Imaging</td>
<td>Isointense in relation to liver</td>
<td>Hyperintense in relation to liver</td>
<td>Markedly hyperintense in relation to liver</td>
<td>Hyperintense in relation to liver</td>
</tr>
</tbody>
</table>

Neuroradiology

Modalities
- CT is the modality of choice for most neuropathology; even under circumstances when MRI is preferred, CT is frequently the initial study performed because of its speed, availability, and lower cost
  - acute head trauma: CT is best for visualizing “bone and blood”; MRI is used only when CT fails to detect an abnormality despite strong clinical suspicion
  - acute stroke: MRI ideal, CT most frequently used
  - suspected subarachnoid or intracranial hemorrhage
  - meningitis: rule out mass effect (e.g. cerebral herniation, shift) prior to lumbar puncture
  - tinnitus and vertigo: CT and MRI are used in combination to detect bony abnormalities and CN VIII tumours, respectively

Figure 26. Epidural hematoma
**Skull Films**
- rarely performed, generally not indicated for non-penetrating head trauma
- **indications**: screening for destructive bony lesions (e.g. metastases), metabolic disease, skull anomalies, post-operative changes and confirmation of hardware placement, skeletal surveys

**CT**
- **indications**: excellent study for evaluation of bony and intracranial abnormalities
- often done first without and then with IV contrast to show vascular structures or anomalies
- vascular structures and areas of blood-brain barrier impairment are opaque (e.g. hyperattenuating or white/show enhancement) with contrast injection
  - when in doubt, look for circle of Willis or confluence of sinuses to determine presence of contrast enhancement
- posterior fossa can be obscured by extensive bony-related streak artifact
- rule out skull fracture, epidural hematoma (lenticular shape), subdural hematoma (crescentic shape), subarachnoid hemorrhage, space occupying lesion, hydrocephalus, and cerebral edema
- multiplanar imaging can be performed with newer generation of multidetector CT scanners

**Myelography**
- introduction of water-soluble, low-osmotic contrast media into subarachnoid space using lumbar puncture followed by x-ray or CT scan
- **indications**: excellent study for disc herniations, traumatic nerve root avulsions, patients with contraindication to MRI

**MRI**
- **indications**: shows brain and spinal soft tissue anatomy in fine detail, clearly distinguishes white from grey matter (especially T1-weighted series), multiplanar reconstruction helpful in pre-operative assessment

**Cerebral Angiography/CT Angiography/MR Angiography**
- **indications**: evaluation of vascular lesions such as atherosclerotic disease, aneurysms, vascular malformations, arterial dissection
- conventional DSA remains the gold standard for the assessment of neck and intracranial vessels; however, it is an invasive procedure requiring arterial (femoral) puncture; catheter manipulation has risk of vessel injury (e.g. dissection, occlusion, vasospasm, emboli)
- MRA methods (phase contrast, time of flight, gadolinium-enhanced) and CTA are much less invasive without actual risk to intracranial or neck vessels
- MRA and CTA are often used first as ‘screening tests’ for the assessment of subarachnoid hemorrhage, vasospasm, aneurysms

**Nuclear Medicine**
- SPECT using $^{99m}$Tc-exametazime (HMPAO) and $^{99m}$Tc-bicisate (ECD) imaging assesses cerebral blood flow by diffusing rapidly across the blood brain barrier and becoming trapped within neurons proportional to cerebral blood flow
- $^{18}$FDG PET imaging assesses cerebral metabolic activity
- **indications**: differentiation of residual tumour vs. radiation necrosis; localizing of epileptic seizure foci; evaluation of atypical dementia
Approach to CT Head

- think anatomically, work from superficial to deep
- scan: confirm that the imaging is of the correct patient, whether contrast was used, if the patient is aligned properly, if there is artifact present
- skin/soft tissue: examine the soft tissue superficial to the skull, looking for thickening suggestive of hematoma or edema; also evaluate the ear, orbital contents (globe, fat, muscles), parotid, muscles of mastication (masseter, temporalis, pterygoids), visualized pharynx
- bone and airspace (use the bone window): check calvarium, visualize mandible, visualize C-spine (usually C1 and maybe part of C2) for fractures, absent bone, lytic/sclerotic lesions; inspect sinuses and mastoid air cells for opacity that may suggest fluid, pus, blood, tumour, or fracture; status of the orbital floor in cases of facial trauma (coronal series best)
- dura and subdural space: crescent-shaped hyperdensity in the subdural space suggests subdural hematoma; lentiform hyperdensity in the epidural space suggests epidural hematoma; check symmetry of dural thickness, where increased thickness may suggest the presence of blood
- parenchyma: asymmetry of the parenchyma suggests midline shift; poor contrast between grey and white matter suggests possible infarction, tumour, edema, infection, or contusion; hyperdensity in the parenchyma suggests enhancing lesions, intracerebral hemorrhage, or calcification; central grey matter nuclei (e.g. globus pallidus, putamen, internal capsule) should be visible, otherwise, suspect infarct, tumour, or infection
- ventricles/sulci/cisterns: examine position of ventricles for evidence of midline compression/shift; hyperdensities in the ventricles suggest ventricular/subdural hemorrhage; enlarged ventricles suggest hydrocephalus; obliteration of sulci may suggest presence of edema causing effacement, possible blood filling in the sulci, or tumour; cistern hyperdensities may suggest blood, pus, or tumour

Selected Pathology

- see Neurosurgery, NS4 for intracranial mass lesions
- see Neurosurgery, NS29 and Plastic Surgery, PL28 for head trauma
- see Emergency Medicine, ER9 for vertebral trauma
- see Neurosurgery, NS27 and Orthopedics, OR23 for degenerative spinal abnormalities

Cerebrovascular Disease (see Neurology, N46 and Neurosurgery, NS17)

- pathogenesis of stroke: see Neurology, N46
- best imaging modality: infarcts best detected by MRI > CT
- findings of infarction
  - early changes
    - CT
      - usually normal within 6 h of infarction
      - edema (loss of grey-white matter differentiation – “insular ribbon” sign, effacement of sulci, mass effect)
      - within 24 h, development of low-density, wedge-shaped area of infarction extending to periphery (correlating to vascular territory distal to affected artery)
      - in case of ischemic stroke, may see hyperattenuating (bright) artery (hyperdense MCA sign) representing intravascular thrombus or embolus
      - in case of hemorrhagic stroke or transformation (common in basal ganglia and cortex), may see bright acute blood surrounded by edema
    - MRI
      - edema with high signal on T2-weighted images and FLAIR image (loss of grey-white matter differentiation, effacement of sulci, mass effect)
      - DWI shows acute high signal changes demonstrating restricted movement of water indicative of cytotoxic edema; usually indicates stroke damage before CT
      - apparent diffusion coefficient image shows low signal intensity in acute ischemia (nadir 3-5 d, returns to baseline 1-4 wk)
  - subacute changes on CT and MRI
    - edema and mass effect more prominent
  - gyral enhancement with contrast indicative of blood-brain barrier breakdown
  - chronic changes on CT and MRI
    - encephalomalacia (parenchymal volume loss) with dilatation of adjacent ventricles
  - carotid artery disease
    - best imaging modality: Duplex Doppler U/S
    - other modalities: MRA or CTA if carotid angioplasty or endarterectomy is under consideration (conventional angiography reserved for inadequate MRA or CTA)
Multiple Sclerosis (refer to Neurology, N51)
- best imaging modality: MRI has high sensitivity in diagnosing MS (>90%) but low specificity (71-74%)
- findings
  - characteristic lesion on MRI is cerebral or spinal plaque
  - plaques typically found in periventricular region, corpus callosum (arranged at right angles to the corpus callosum), centrum semiovale, and to a lesser extent in deep white matter structures and basal ganglia
  - “Dawson’s fingers” refers to perivenular regions of demyelination that are seen to radiate outwards into the deep periventricular region
  - plaques usually have ovoid appearance, hyperintense on T2 and hypointense on T1
  - conventional T2 may underestimate plaque size and overall plaque burden – advanced techniques (diffusion tensor imaging and MR spectroscopy) can be of use
  - perivascular and interstitial edema may be prominent
  - spinal cord lesions typical of MS
    - little or no cord swelling
    - unequivocal hyperintensity on T2-weighted sequences
    - size at least 3 mm but less than 2 vertebral segments in length
    - occupy only part of the cord in cross-section
    - focal (i.e. clearly delineated and circumscribed on T2-weighted sequences)

CNS Infections
- leptomenigitis
  - pathogenesis: inflammation of the pia or arachnoid mater, most often secondary to hematogenous spread from infection or via organisms gaining access across areas not protected by the blood-brain barrier (choroid plexus or circumventricular organs)
  - pathogens include: S. pneumoniae, H. influenzae, N. meningitidis, L. monocytogenes
  - best imaging modality: MRI (T2-weighted/FLAIR) superior to CT
  - findings
    - meningeal enhancement (following the gyri/sulci, and/or basal cisterns), hydrocephalus (communicating), cerebral swelling, subdural effusion
    - a normal MRI does not rule out leptomeningitis
- herpes simplex encephalitis (see Infectious Diseases, ID18)
  - pathogenesis: inflammation of the brain parenchyma secondary to infection with herpes simplex virus, asymmetrically affects the limbic regions of the brain (i.e. temporal lobes, orbitofrontal region, insula, and cingulate gyrus)
  - best imaging modality: MRI (T1- and T2-weighted)
  - findings
    - acute (within 4-5 d): asymmetric high intensity lesions on T2 MRI in temporal and inferior frontal lobes strongly suggestive
    - DDx: infarct, tumour, status epilepticus, limbic encephalitis
    - CT may show low density in temporal lobe and insula; rarely basal ganglia involvement
    - long-term may show parenchymal loss to affected areas
- cerebritis/cerebral abscess
  - pathogenesis: an infection of the brain parenchyma (cerebritis) which can progress to a collection of pus (abscess), most frequently due to hematogenous spread of infectious organisms, commonly located in the distribution of the MCA
  - pathogens include: S. aureus (often in IV drug users, nosocomial), Streptococcus, Gram negative bacteria, Bacteroides
  - best imaging modality: MRI including DWI imaging series (abscess will be DWI positive); CT still used as a viable alternative
  - findings according to one of four stages of abscess formation
    - early cerebritis (1-3 d): inflammatory infiltrate with necrotic centre, low intensity on T1, high intensity on T2
    - late cerebritis (4-9 d): ring enhancement may be present
    - early capsule (10-13 d): ring enhancement
    - late capsule (14 d or greater): well demarcated ring-enhancing lesion, low intensity core, with mass effect; considerable edema around the lesion, seen as hyperintensity on T2
Musculoskeletal System

Modalities

- refer to MI2 for advantages and disadvantages of the following imaging modalities

Plain Film/X-Ray
- usually initial study used in evaluation of bone and joint disorders
- indications: fractures and dislocations, arthritis, assessment of malalignment, orthopedic hardware, and bone tumours (initial)
- minimum of two films orthogonal to each other (usually AP and lateral) to rule out a fracture
- image proximal and distal joints (particularly important with paired bones (e.g. radius/ulna)
- minimally effective in evaluating soft tissue injury

CT
- evaluation of fine bony detail
- indications: assessment of complex, comminuted, intra-articular or occult fractures including distal radius, scaphoid, skull, spine, acetabulum, calcaneus, and sacrum
- evaluation of soft tissue calcification/ossification

MRI
- indications: evaluation of internal derangement of joints (e.g. ligaments, joint capsule, menisci, labrum, cartilage), assessment of tendons and muscle injuries, characterization and staging of soft tissue and bony masses

Ultrasound
- indications: tendon injury (e.g. rotator cuff, Achilles tendon), detection of soft tissue masses and to determine whether cystic or solid, detection of foreign bodies, U/S guided biopsy and injections
- Doppler determines vascularity of structures

Nuclear Medicine (Bone Scintigraphy)
- determine the location and extent of bony lesions
- $^{99m}$Tc-methylene diphosphonate localizes to areas of increased bone turnover or calcification – growth plate in children, tumours, infections, fractures, metabolic bone disease (e.g. Paget's), sites of reactive bone formation, and periostitis
- advantages: very sensitive, capable of imaging entire body with relatively low dose radiation
- disadvantages: low specificity, not widely available due to special requirements (e.g. gamma camera, radiopharmaceuticals)

Approach to Bone X-Rays

- identification: name, MRN, age of patient, type of study, region of investigation
- soft tissues: swelling, calcification/ossification
- joints: alignment, joint space, presence of effusion, osteophytes, erosions, bone density, overall pattern, and symmetry of affected joint
- bone: periosteum, cortex, medulla, trabeculae, density, articular surfaces, bone destruction, bone production, appearance of the edges or borders of any lesions

Trauma

Fracture/Dislocation
- description of fractures
- site of fracture (bone, region of bone, intra-articular vs. extra-articular)
- pattern of fracture line (simple vs. comminuted)
- displacement (distal fragment with reference to the proximal fragment)
- soft tissue involvement (calcification, gas, foreign bodies)
- type of fracture (stress vs. pathologic)
- for specific fracture descriptions and characteristics of fractures, see Orthopedics, OR5
Arthritis

Radiographic Hallmarks of Osteoarthritis
- joint space narrowing – typically non-uniform
- subchondral sclerosis
- subchondral cyst formation
- osteophytes

Radiographic Hallmarks of Rheumatoid Arthritis
- joint space narrowing – typically uniform
- soft tissue swelling
- erosions
- periarticular osteopenia

Bone Tumour

Approach
- metastatic tumours to bone are much more common than primary bone tumours, particularly if age >40 yr
  - diagnosis usually requires a biopsy if primary not located
  - few benign tumours/lesions have potential for malignant transformation
  - MRI is good for tissue delineation and pre-operative assessment of surrounding soft tissues, neurovascular structures, and medullary/marrow involvement
  - plain film is less sensitive than other modalities but useful for assessing aggressiveness and constructing differential diagnosis

Considerations and Tumour Characteristics
- for specific bone tumours, see Orthopedics, OR46
- age – most common tumours by age group
  - <1 yr of age: metastatic neuroblastoma
  - 1-20 yr of age: Ewing’s sarcoma in tubular bones
  - 10-30 yr of age: osteosarcoma and Ewing’s tumour in flat bones
  - >40 yr of age: metastases, multiple myeloma, and chondrosarcoma
- multiplicity: metastases, myeloma, lymphoma, fibrous dysplasia, enchondromatosis
- location within bone
  - epiphysis: giant cell tumour, chondroblastoma, geode, eosinophilic granuloma, infection
  - metaphysis: simple bone cyst, aneurysmal bone cyst, enchondroma, chondromyxoid fibroma, nonossifying fibroma, osteosarcoma, chondrosarcoma
  - diaphysis: fibrous dysplasia, aneurysmal bone cyst, brown tumours, eosinophilic granuloma, Ewing’s sarcoma
- expansile
  - aneurysmal bone cyst, giant cell tumour, enchondromas, brown tumours, metastases (especially renal and thyroid), plasmacytoma
- matrix mineralization
  - chondroid (popcorn calcification) or osseous
- margin/zone of transition: area between lesion and normal bone
  - cortex: intact, disturbed
  - periosteal reaction
  - soft tissue mass

Figure 38. Rheumatoid arthritis (A) compared with osteoarthritis (B) changes on X-ray

Benign Lesions which may have Aggressive Features
- Osteomyelitis
- Osteoblastoma
- Aneurysmal bone cyst
- Langerhans cell histiocytosis
- Myositis ossificans

Periosteal Reaction
- “Onion skinning” = Ewing’s sarcoma
- “Sunburst”, “hair on end” = osteosarcoma
- “Codman’s triangle” = osteosarcoma, Ewing’s sarcoma, subperiosteal abscess

Table 18. Characteristics of Benign and Malignant Bone Lesions

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thin sclerotic margin/sharp delineation of lesion</td>
<td>Poor delineation of lesion – wide zone of transition</td>
</tr>
<tr>
<td>Overlying cortex intact</td>
<td>Loss of overlying cortex/bony destruction</td>
</tr>
<tr>
<td>No or simple periosteal reaction</td>
<td>Periosteal reaction</td>
</tr>
<tr>
<td>No soft tissue mass</td>
<td>Soft tissue mass</td>
</tr>
</tbody>
</table>
Metastatic Bone Tumours
- all malignancies have potential to metastasize to bone
- metastases are 20-30x more common than primary bone tumours
- metastasis can cause a lytic or a sclerotic reaction when seeding to bone
- when a primary malignancy is first detected, a bone scan is often part of the initial workup
- may present with pathological fractures or pain
- biopsy or determination of primary is the only way to confirm the diagnosis
- most common metastatic bone tumours: breast, prostate, lung, see Orthopedics, OR46

Table 19. Characteristic Bone Metastases of Common Cancers

<table>
<thead>
<tr>
<th>Lytic</th>
<th>Sclerotic</th>
<th>Expansile</th>
<th>Peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast</td>
<td>Prostate</td>
<td>Thyroid</td>
<td>Kidney</td>
</tr>
<tr>
<td>Lung</td>
<td>Breast</td>
<td>Renal</td>
<td>Lung</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Lymphoma</td>
<td>Thyroid</td>
<td>Melanoma</td>
</tr>
<tr>
<td>Kidney</td>
<td>Lung</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td>Bovet</td>
<td>Medulloblastoma</td>
<td>(KLM: flies to the periphery)</td>
</tr>
<tr>
<td>Treated tumours</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Infection

Osteomyelitis
- MRI is the imaging modality of choice for demonstrating bone, bone marrow, and soft tissue abnormalities
- ⁹⁹ᵐTc, followed by ¹¹¹In labeled white cell scan or gallium radioisotope scan
- plain film changes visible 8-10 d after process has begun
  - soft tissue swelling
  - local periosteal reaction
  - pockets of air (from anaerobes) may be seen in the tissues, may also suggest necrotizing fasciitis
  - mottled and nonhomogeneous with a classic “moth-eaten” appearance
  - cortical destruction

Bone Abscess
- overlying cortex has periosteal new bone formation
- sharply outlined radiolucent area with variable thickness in zone of transition
- variable thickness periosteal sclerosis
- sequestrum: a piece of dead bone within a Brodie's abscess
- a sinus tract or cloaca may communicate between the abscess through the cortex to the surface of the bone
- best modality: MRI for bone, bone marrow, and soft tissue abnormalities; CT for sequestra and cortical erosions

Metabolic Bone Disease

Osteoporosis
- reduction in amount of normal bone mass; fewer and thinner trabeculae; diffuse process affecting all bones
- DEXA: gold standard for measuring bone mineral density
  - T-score: the number of standard deviations from the young adult mean, most clinically valuable
    - osteopenia: $-2.5 < T\text{-score} < -1$
    - osteoporosis: $T\text{-score} \leq -2.5$
  - Z-score: the number of standard deviations from the age-matched mean
  - risk of fracture: related to bone mineral density, age, history of previous fractures, steroid therapy
  - diagnostic sensitivity of DEXA highest when bone mineral density measured at lumbar spine and proximal femur
- appearance on plain film
  - osteopenia: reduced bone density on plain films
  - may also be seen with osteomalacia, hyperparathyroidism, and disuse
  - compression of vertebral bodies
  - biconcave vertebral bodies (“codfish” vertebrae)
  - long bones have appearance of thinned cortex and increased medullary cavity
  - look for complications of osteoporosis (e.g. insufficiency fractures: hip, vertebrae, sacrum, pubic rami)
- see Endocrinology, E38
Osteomalacia/Rickets
- reduction in bone mineral density; normal amount of bone, but reduced mineralization of normal osteoid
- usually due to vitamin D deficiency, resulting in softening and bowing of long bones
- similar to osteoporosis, initial radiological appearance of osteopenia (coarse and poorly defined bone texture)
- “fuzzy”, ill-defined trabeculae
- Looser’s zones (pseudofracture)
  - characteristic radiologic feature
  - fissures or clefs at right angles to long bones and extending through cortex
  - DDx: chronic renal disease, fibrous dysplasia, hyperthyroidism, Paget's, osteodystrophy, X-linked hypophosphataemia

Hyperparathyroidism
- most common cause is renal failure (secondary hyperparathyroidism)
- chondrocalcinosis
  - calcium crystal deposition in hyaline cartilage or fibrocartilage (including arteries and periarticular soft tissue)
  - resorption of bone typically in hands (subperiosteal and at tufts), sacroiliac joints (subchondral), skull (“salt and pepper” appearance), osteoclastoma (brown tumours)
  - “rugger jersey spine”: band-like osteosclerosis at superior/inferior margins of vertebral bodies
- see Endocrinology, E38

Paget’s Disease
- abnormal remodeling involving single or multiple bones – especially skull, spine, pelvis
- 3 phases: 1st phase = lytic, 2nd phase = mixed (lytic/sclerotic), 3rd phase = sclerotic
- features
  - coarsening of the trabeculae with bone expansion
  - bone softening/bowing
  - bone scan will reveal high activity, especially at bone ends
  - thickened cortex
- see Endocrinology, E42
Brain

- $^{99m}$Tc-exametazime (HMPAO) and $^{99m}$Tc-bicisate (ECD) imaging used in SPECT to assess cerebral blood flow and cellular metabolism, taken up predominantly in grey matter; used for dementia, traumatic brain injury and to a lesser extent vasculitis, neuropsychiatric disorders and occasionally stroke; also the most commonly used tracers to confirm brain death (i.e. absent blood flow to the brain and absent uptake on delayed planar and SPECT images in brain and brainstem, assuming study is technically adequate); either tracer can be used for seizure imaging to assess for the most likely location of epileptogenic focus but usually must be made available for 24 hr and the patient followed by a nurse who is competent to administer the activity at the time of seizure.

- PET imaging assesses metabolic activity most commonly with $^{18}$FDG; used for dementia imaging, grade and stage of brain tumours, occasionally for seizure disorder imaging, and vasculitis; PET imaging with amyloid tracers for diagnosis of Alzheimer’s disease is becoming more common.

- CSF imaging, intrathecal administration of $^{111}$In DTPA to evaluate CSF leak or to differentiate normal pressure hydrocephalus from brain atrophy.

- CSF shunt evaluation for obstruction (most commonly ventriculoperitoneal) with sterile or pyrogen free $^{99m}$Tc (usually) or $^{111}$In-DTPA; small quantity of activity is injected into the reservoir under sterile conditions and should flow freely into the peritoneal cavity by 45 min; maneuvers such as pumping the shunt, sitting the patient upright or ambulating are acceptable to encourage flow during this time.

- Adrenergic imaging of the heart with MIBG has been used to differentiate dementias with autonomic dysfunction (i.e. Lewy Body and Parkinson’s disease) from other forms of dementia (i.e. autonomic impairment associated with decreased MIBG activity in the heart).

Thyroid

Radioactive Iodine Uptake (see Endocrinology, E20)

- index of thyroid function (trapping and organification of iodine)
- radioactive $^{131}$I given PO to fasting patient (small quantity)
- measure percentage of administered iodine taken up by thyroid
- increased RAU: toxic multinodular goitre, toxic adenoma, Graves’ disease
- decreased RAU: subacute thyroiditis, late Hashimoto’s disease, exogenous thyroid hormone or iodine, falsely decreased in patient with recent radiographic contrast studies, high dietary iodine (e.g. seaweed, taking a “thyroid vitamin”)
- Important – iodine uptake helps in the differential of hyperthyroidism only, not hypothyroidism (exception is pediatrics)

Thyroid Imaging (Scintiscan)

- $^{99m}$Tc-pertechnetate IV or radioactive iodine ($^{123}$I); most Canadian sites use pertechnetate to reduce cost
- provides functional anatomic detail
- hot (hyperfunctioning) lesions: usually benign (e.g. adenoma, toxic multinodular goitre), cancer very unlikely (less than 1%)
- cold (hypofunctioning) lesions: cancer must be considered until biopsy negative even though only 6-10% are cancerous; decision to biopsy should be based on clinical and sonographic features
- isointense i.e. “warm” lesions: cancer must be considered as an isointense lesion may represent cold nodules superimposed on normal tissue; if cyst suspected, correlate with U/S

Radioiodine Ablation

- $^{131}$I for Graves’ disease, multinodular goitre, thyroid cancer (in the case of thyroid cancer, ablation performed at higher dose and after thyroidectomy)
- serum thyroglobulin used to detect recurrent thyroid cancer in a patient that has received ablation
- advice should be given for patient-specific precautions to remain away from family members and caregivers to reduce radiation exposure after thyroid ablation, do not initiate pregnancy for 6 mo, small risk of exophthalmos, thyroid storm, secondary malignancy

Pediatric Hypothyroidism

- Pertechnetate thyroid scan can differentiate thyroid agenesis, hemiagenesis, lingular thyroid, organification defect, however should not wait for a diagnosis to start thyroid hormone replacement in a neonate; start immediately.
Respiratory

V/Q Scan
examine areas of lung in which ventilation and perfusion do not match

- ventilation scan
  - patient breathes radioactive gas (nebulized 99mTc-DTPA, 133Xe, or most commonly Technegas) through a closed system, filling alveoli proportionally to ventilation
  - ventilation scan defects indicate: airway obstruction (i.e. air trapping), chronic lung disease, bronchospasm, tumour mass obstruction

- perfusion scan
  - radiotracer injected IV (99mTc-MAA) → trapped in pulmonary capillaries (0.1% of arterioles occluded) according to blood flow
  - relatively contraindicated in severe pulmonary HTN, right-to-left shunt, previous history of pneumonectomy, small child. In these cases fewer particles are usually given
  - to rule out PE
    - indications: some institutions favour in pregnancy (lower radiation dose to breast than CT), or where CT contrast contraindicated (e.g. contrast allergy, renal failure)
    - areas of lung are well ventilated but not perfused (unmatched defect) are suspicious for acute infarction
    - defects are wedge-shaped, extend to periphery, usually bilateral and multiple
    - often reported as high probability (>2 large i.e. segmental mismatched perfusion defects), intermediate, low, very low, or normal according to modified PIOPED II criteria although now are increasingly reported as PE present, indeterminate or normal
    - useful in finding clinically important emboli
    - decreased detection of incidentalalomas commonly found on CT
  - not valid for assessment of PE when patients have consolidation and the test can be limited by ventilatory problems (e.g. COPD), much like CT
  - modified V/Q scan (perfusion only, lower dose contrast) may be used for pregnant patients if CXR is normal or if there are ventilatory problems

Cardiac

Myocardial Perfusion Scanning
- to investigate coronary artery disease (CAD), assess treatment of CAD, pre op risk stratification, viability testing
- 99mTc-sestamibi, or 99mTc-tetrofosmin are used most commonly, thallium 201 was used previously but largely discontinued due to high radiation doses to patients and unfavourable imaging characteristics; today thallium still used for viability studies
- injected at peak exercise (85% max predicted heart rate by the Bruce protocol, chest pain, ECG changes) or after persantine challenge (vasodilator), or dobutamine infusion (chronotropic, again to 85% predicted heart rate); can be done as stress only protocol with optional rest or as stress and rest combined protocol (i.e. as 1 day or 2 day protocol).
- patients with left bundle usually given pharmacologic stress because EKG is difficult to interpret for ST changes and avoids a characteristic artifact
- pharmacologic stress contraindicated if BP is < 90 systolic; persantine exacerbates asthma, so patients with asthma and wheeze who cannot exercise usually get dobutamine infusion; reverse persantine with aminophylline or caffeine
- persistent defect (at rest and stress) suggests infarction or myocardial scar; reversible defect (only during stress) suggests ischemia
- used to discriminate between reversible (ischemia) vs. irreversible (infarction) changes when other investigations are equivocal
- Courage trial indicates that patients with >10% ischemic myocardium benefit most from revascularization
- see Cardiology and Cardiac Surgery, C13

Radionuclide Ventriculography
- 99mTc tagged to red blood cells, tagged albumin is also acceptable
- first pass through RV → pulmonary circulation → LV; provides information about RV function, presence of shunts
- cardiac MUGA scan sums multiple cardiac cycles, usually at least 200 beats
- evaluation of LV function and regional wall motion, ejection fraction
- images are obtained by gating (synchronizing) the count acquisitions to the ECG signal
- can assess diastolic dysfunction
- provides information on ejection fraction (normal = 50-65%), ventricular volume, and wall motion
- indications: most commonly to monitor potential cardiac toxicity with chemotherapy or herceptin, as a gold standard of ejection fraction in defibrillator work up
HIDA Scan (Cholescintigraphy)
- IV injection of $^{99m}$Tc-disofenin (DISIDA) or $^{99m}$Tc-mebrofenin which is bound to protein, taken up, and excreted by hepatocytes into biliary system.
- can be performed in non-fasting state but prefer NPO after midnight
- indicated in workup of cholecystitis when abdominal ultrasound result is equivocal:
  - acute cholecystitis: no visualization of gallbladder at 4 h or 1 hour after administration of morphine
  - chronic cholecystitis: no visualization of gallbladder at 1 h but seen at 4 h or after morphine administration
- gallbladder visualized when cystic duct is patent (rules out acute cholecystitis with >99% certainty), usually seen by 30 min to 1 h
- differential diagnosis of obstructed cystic duct: acute/chronic cholecystitis, decreased hepatobiliary function (commonly due to alcoholism), bile duct obstruction, parenteral nutrition, fasting less than 4 h or more than 24 h
- also used to assess bile leaks post-operatively or in trauma
- gallbladder ejection fraction (>38% is normal) can be measured after a fatty meal or CCK to assess for biliary dyskinesia

RBC Scan
- IV injection of radiotracer with sequential images of the abdomen ($^{99m}$Tc RBCs)
- GI bleed
  - if bleeding acutely at <0.5 mL/min, the focus of activity in the images generally indicates the site of the acute bleed, look for a change in shape and location on sequential image, requires active bleeding to localize
  - if bleeding acutely at >0.5 mL/min, use angiography (more specific)
- liver lesion evaluation
  - hemangioma has characteristic appearance: cold early (limited blood flow to lesion), fills in later (accumulation of tagged cells greater than surrounding liver parenchyma)

Other Important Nuclear Medicine Abdominal Tests
- Meckel's Scan: uses Tc 99m pertechnetate; give patient ranitidine premedication; Meckel's diverticulum contains gastric mucosa which will light up at the same time as the stomach and get brighter with time like stomach
- Indium 111 octreoscan: a somatostatin analog used for evaluation and staging of neuroendocrine tumours including carcinoid; gastrinoma and carcinoid tend to be more octreotide avid than insulinoma.
- Iodinated MIBG: a norepinephrine analog, used for pheochromocytoma, neuroblastoma and medullary thyroid cancer most commonly; limited cardiac applications as above
- solid and liquid gastric emptying: a standardized solid or liquid meal is labelled, usually with Tc 99m sulfur colloid and gastric emptying studied over time. There are normal ranges for solids and liquids

Urea Breath Test
- indication: diagnosis of gastric Helicobacter pylori infection
- patient administered $^{14}$C-labelled urea orally, urea metabolized by H. pylori to ammonia and $^{14}$CO$_2$. $^{14}$C-labeled CO$_2$ is measured via plastic filament detectors or liquid scintillation

Functional Renal Imaging
- evaluation of renal function and anatomy using $^{99m}$Tc DTPA or Tc 99m MAG3
- frequently used to provide index of relative function between two kidneys
- frequently used in adults to assess for UPJ obstruction (by assessing the clearance half time with lasix), and assess renal transplants or as a nuclear GFR study in patients wanting to donate kidneys
- in children, imaging with Tc 99m DMSA is used to assess for pyelonephritis
- in children, the injection of tracer into the bladder via foley catheter is often used to assess for reflux

Bone Scan
- isotopes, usually $^{99m}$Tc-diphosphonate
- radioactive tracer binds to hydroxyapatite of bone matrix
- increased binding when increased blood supply to bone and/or high bone turnover (active osteoblasts)
- indications: bone pain of unknown origin, staging or restaging of cancer with boney mets (or primary bone cancer), imaging of arthroplasty complications like loosening or infection, osteomyelitis imaging
when used to assess for osteomyelitis, usually done in combination with gallium or white blood cell scan
- differential diagnosis of positive bone scan: bone metastases (breast, prostate, lung, thyroid), primary bone tumour, arthritis, fracture, infection, anemia, Paget’s disease
- lytic lesions like multiple myeloma, renal cell cancer, eosinophilic granuloma: typically normal or cold (false negative); need a skeletal survey
- “superscan”: increased bone uptake and poor renal uptake due to diffusion
- infiltration of prostate or metabolic causes (i.e. renal osteodystrophy)

**Interventional Radiology**

**Vascular Procedures**

**Angiography**
- injection of contrast material through a catheter placed directly into an artery or vein to delineate vascular anatomy
- catheter can be placed into a large vessel (e.g. aorta, vena cava) for a “fluor” or selectively placed into a branch vessel for more detailed examination of smaller vessels and specific organs
- indications: diagnosis of primary occlusive or stenotic vascular disease, aneurysms, coronary, carotid and cerebral vascular disease, PE, trauma, bleeding (GI, hemoptysis, hematuria), vascular malformations, as part of endovascular procedures (endovascular aneurysm repair, thrombolysis, stenting, and angioplasties)
- complications (<5% of patients): puncture site hematoma, infection, pseudoaneurysm, AV fistula, dissection, thrombosis, embolic occlusion of a distal vessel
- due to improved technology, non-invasive evaluation of vascular structures is being performed more frequently (colour Doppler U/S, CTA, and MRA)
- see Neuroradiology, MI18

**Percutaneous Transluminal Angioplasty and Stents**
- introduction and injection of a balloon into a stenosed or occluded vessel to restore distal blood supply
- common alternative to surgical bypass grafting with 5-yr patency rates similar to surgery, depending on site
- renal, iliac, femoral, mesenteric, subclavian, coronary, and carotid artery stenoses are amenable to treatment
- vascular stents may help improve long-term results by keeping the vessel wall patent after angioplasty
- stents are also used for angioplasty failure or complications
- stent grafts (metal mesh covered with durable fabric) may provide an alternative treatment option for aneurysms and AV fistulas
- complications: similar to angiography, but also includes vessel rupture

**Thrombolytic Therapy**
- may be systemic (IV) or catheter directed
- infusion of a fibrinolytic agent (urokinase, streptokinase, TNK, tPA – used most commonly) via a catheter inserted directly into a thrombus
- can restore blood flow in a vessel obstructed with a thrombus or embolus
- indications: treatment of ischemic limb (most common indication), early treatment of MI or stroke to reduce organ damage, treatment of venous thrombosis (DVT or PE)
- complications: bleeding, stroke, distal embolus, reperfusion injury with myoglobinuria and renal failure if advanced ischemia present

**Embolization**
- injection of occluding material into vessels
- permanent agents: amplatzers plugs, coils, glue, and onyx
- temporary: gel foam, autologous blood clots
- indications: management of hemorrhage (epistaxis, trauma, GI bleed, GU bleed), treatment of arteriovenous malformation, pre-operative treatment of vascular tumours (bone metastases, renal cell carcinoma), varicocele embolization for infertility, symptomatic uterine fibroids
- complications: post-embolization syndrome (pain, fever, leukocytosis), unintentional embolization of a non-target organ with resultant ischemia

**Inferior Vena Cava Filtre**
- insertion of metallic “umbrellas” to mechanically trap emboli and prevent PE
- may be temporary (retrievable) or permanent
- inserted via femoral vein, jugular vein, or antecubital vein
- usually placed infrarenally to avoid renal vein thrombosis
- indications: contraindication to anticoagulation, failure of adequate anticoagulation (e.g. recurrent PE despite therapeutic anticoagulant levels), complication of anticoagulation
Central Venous Access
- variety of devices available
  - PICC, external tunneled catheter (Hickman or dialysis catheters), subcutaneous port (Portacath®)
  - indications: chemotherapy, TPN, long-term antibiotics, administration of fluids and blood products, blood sampling
  - complications: venous thrombosis and central venous stenosis, infection including sepsis, pneumothorax

Nonvascular Interventions

Percutaneous Biopsy
- replaces open surgical procedure
- many sites are amenable to biopsy using U/S, fluoroscopy, CT or MR guidance
- complications: false negative (sampling error or tissue necrosis), pneumothorax in 30% of lung biopsies (chest tube required in ~5%), acute pancreatitis (pancreatic biopsies), bleeding from liver biopsies in patients with uncorrectable coagulopathies or ascites (can be minimized with transjugular approach)

Abscess Drainage
- placement of a drainage catheter into an infected fluid collection
- administer broad spectrum IV antibiotics prior to procedure
- routes: percutaneous (most common), transgluteal, transvaginal, transrectal
- complications: hemorrhage, injury to intervening structures (e.g. bowel), bacteremia, sepsis

Percutaneous Biliary Drainage/Cholecystostomy
- placement of drainage catheter ± metallic stent into obstructed biliary system (PBD) or gallbladder (cholecystostomy) for relief of jaundice or infection
- percutaneous gallbladder access can be used to crush or remove stones
- indications
  - cholecystostomy: acute cholecystitis
  - PBD: biliary obstruction secondary to stone or tumour, cholangitis
- complications
  - acute: sepsis, hemorrhage
  - long-term: tumour ingrowth and stent occlusion

Percutaneous Nephrostomy
- placement of catheter into renal collecting system
- indications: hydronephrosis, pyonephrosis, ureteric injury with or without urinary peritonitis (traumatic or iatrogenic)
- complications: bacteria and septic shock, hematuria due to pseudoaneurysm or AV fistulas, injury to adjacent organs

Gastrostomy/Gastrojejunostomy
- percutaneous placement of catheter directly into either stomach (gastrostomy) or through stomach into small bowel (transgastric jejunostomy)
- indications: inability to eat (most commonly CNS lesion e.g. stroke) or esophageal obstruction, decompression in gastric outlet obstruction
- complications: gastrosophageal reflux with aspiration, peritonitis, hemorrhage, bowel or solid organ injury

Radiofrequency Ablation
- U/S or CT guided probe is inserted into tumour, radiofrequency energy delivered through probe causes heat deposition and tissue destruction
- indications: hepatic tumours (HCC and metastases), renal tumours
- complications: destruction of neighbouring tissues and structures, bleeding
Breast Imaging

Modalities

Mammography

Description
• x-ray imaging of the breasts for screening in asymptomatic patients, or diagnosis of clinically-detected or screening-detected abnormalities (see General Surgery, GS54)
• routine evaluation involves two standard views: cranio-caudal and medial-lateral-oblique

Indications
• screening
  ▪ begin screening from age 50 q2 yr
  ▪ no strong data to support screening >70 yr, but may continue screening if in good general health
  ▪ if <50, screening is only recommended for those with high risk of breast cancer
  ▪ screening detects 2-8 cancers/1,000 women screened
• surveillance
  ▪ follow-up of women with previous breast cancer
• diagnostic: includes mammography with special views and/or ultrasound
  ▪ work-up of an abnormality that may be suggestive of breast cancer including a lump or thickening, localized nodularity, dimpling or contour deformity, a persistent focal area of pain, and spontaneous serous or sanguinous nipple discharge from a single duct
  ▪ women with abnormal screening mammograms
  ▪ suspected complications of breast implants

<p>| Table 20. Breast Imaging Reporting and Data System (BI-RADS®) Mammography Categories |</p>
<table>
<thead>
<tr>
<th>Assessment Categories</th>
<th>Imaging Findings</th>
<th>Follow-Up Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>BI-RADS 0</td>
<td>Incomplete</td>
<td>Additional imaging Comparison to prior films</td>
</tr>
<tr>
<td>BI-RADS 1</td>
<td>Negative</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 2</td>
<td>Benign</td>
<td>Routine screening</td>
</tr>
<tr>
<td>BI-RADS 3</td>
<td>Probably benign Likelihood of malignancy is &lt;2%</td>
<td>Unilateral mammogram at 6 mo</td>
</tr>
<tr>
<td>BI-RADS 4</td>
<td>Suspicious abnormality</td>
<td>Biopsy</td>
</tr>
<tr>
<td>BI-RADS 5</td>
<td>Highly suspicious of malignancy Likelihood of malignancy is 95%</td>
<td>Biopsy</td>
</tr>
<tr>
<td>BI-RADS 6</td>
<td>Malignancy confirmed by biopsy</td>
<td>Definitive therapy</td>
</tr>
</tbody>
</table>

Breast Ultrasound

Indications
• characterization of palpable abnormalities (ultrasound 1st line <30 yr and in lactating and pregnant women, >30 yr need mammogram 1st)
• further characterization of mammographic findings
• guidance for interventional procedures

Breast MRI

Description
• contrast enhanced MRI of the breasts
• sensitive for detecting invasive breast cancer (95-100%) but specificity variable (37-97%)
• for diagnosis, used only after mammography and U/S investigation
• use as a screening modality is limited to high risk patients, in conjunction with mammography

Indications
• “problem solving” of indeterminate findings following complete mammographic and ultrasound work up
• evaluation of patients with suspected silicone implant rupture and problems associated with breast implants
• evaluation of previously diagnosed breast cancer: positive margins, recurrence, response to chemotherapy
• High Risk Screening
  ▪ known BRCA1 or BRCA2 mutation, or other gene predisposing to breast cancer or untested first-degree relative of a carrier of such a gene mutation
  ▪ family history consistent with a hereditary breast cancer syndrome and/or estimated personal lifetime cancer risk >25%
  ▪ high-risk marker on prior biopsy (atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ)
  ▪ radiation therapy to chest (before age 30)
**Breast Interventional Procedures**

**Description**
- Includes fine needle aspirate biopsy, core needle biopsy, stereotactic biopsy, MRI guided biopsy, abscess drainage, and cyst aspiration (see General Surgery, GS54)

**Indications**
- Cystic mass: complex cyst, symptomatic, suspected abscess
- Solid mass: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5)
- Suspicious calcifications: confirm diagnosis of a lesion suspicious for malignancy (BI-RADS® Category 4 or 5) – stereotactic biopsy
- Initial percutaneous biopsy procedure that was insufficient or discordant with imaging
- Percutaneous wire localization of a lesion generally recommended

**Breast MASSES**
- Definition: a space occupying lesion seen in two different projections; if seen in only a single projection it should be called an “asymmetry” until its three-dimensionality is confirmed

**Table 21. Mammographic Features of Benign and Malignant Breast Masses**

<table>
<thead>
<tr>
<th>Shape</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oval, round, lobular</td>
<td>Irregular</td>
<td></td>
</tr>
<tr>
<td>Circumscribed, well-defined</td>
<td>Indistinct, microlobulated, spiculated</td>
<td></td>
</tr>
<tr>
<td>Radiolucent (oil cyst, lipoma, fibrolipoma, galactoceles, hamartoma)</td>
<td>Radiodense</td>
<td></td>
</tr>
</tbody>
</table>

**Calcifications (± mass)**
- Popcorn (fibrinoid adenoma), lucent centred (oil cyst/fat necrosis), layering (milk of calcium), vascular, round, scattered
- Pleomorphic (vary in size and shape), amorphous (indistinct), fine linear, coarse heterogeneous, regional, segmental, clustered

**Other Findings**
- Tubular density/dilated duct: branching tubular structures usually represent enlarged ducts (milk ducts); if they are clearly identified as such, these densities are of little concern
- Intramammary lymph node: typical lymph nodes are circumscribed, reniform and often have a fatty notch and centre; usually less than 1 cm, and usually seen in the outer, often upper part of the breast; when these characteristics (particularly fatty centre or notch) are well seen, the lesion is almost always benign and insignificant
- Focal asymmetry: area of breast density with similar shape on two views, but completely lacking borders and conspicuity of a true mass; must be carefully evaluated with focal compression to exclude findings of a true mass or architectural distortion
  - If focal compression shows mass-like character, or if the area can be palpated, biopsy generally recommended

**References**


Canadian Association of Radiologists (CAR) standard for breast imaging. Ottawa: Canadian Association of Radiologists, 1998.


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   Renal Structure and Function
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Anatomy of the Kidney

- see Urology, U2

Renal Structure and Function

The Nephron
- basic structural and functional unit of the kidney, approximately 1 million per kidney
- 2 main components: glomerulus and attached renal tubule
- direction of blood flow: afferent arteriole → glomerular capillaries → efferent arteriole → vasa recta (the capillaries surrounding the tubules) → renal venules

<table>
<thead>
<tr>
<th>Table 1. Major Functions of the Kidneys</th>
</tr>
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<tbody>
<tr>
<td>Function</td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td>1. Waste Excretion</td>
</tr>
<tr>
<td>Tubular secretion</td>
</tr>
<tr>
<td>Tubular catabolism</td>
</tr>
<tr>
<td>2. Electrolyte Balance and Osmoregulation</td>
</tr>
<tr>
<td>Tubular K+ secretion</td>
</tr>
<tr>
<td>Tubular H+ secretion</td>
</tr>
<tr>
<td>HCO3- synthesis and reabsorption</td>
</tr>
<tr>
<td>Tubular Ce2+, Mg2+, PO43- transport</td>
</tr>
<tr>
<td>Synthesize osmolytes</td>
</tr>
<tr>
<td>3. Hormonal Synthesis</td>
</tr>
<tr>
<td>Vitamin D activation: 25(OH)VitD converted to 1,25(OH)2VitD</td>
</tr>
<tr>
<td>Renin production (juxtaglomerular apparatus)</td>
</tr>
<tr>
<td>4. Blood Pressure Regulation</td>
</tr>
<tr>
<td>Renin production</td>
</tr>
<tr>
<td>5. Glucose Homeostasis</td>
</tr>
</tbody>
</table>

The Glomerulus
- site where blood constituents are filtered through to the kidney tubules for excretion or reabsorption
- filtration occurs across the glomerular filtration barrier (endothelium, GBM, podocytes) into Bowman’s space
- particles are selectively filtered by size (<60 kDa) and charge (negative charge repelled)
- consists of following cell types
  1. Mesangial cells
     - structural cells that support the vascular tree; they are also contractile and produce vasoactive substances to help control blood flow
  2. Capillary endothelial cells
     - one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their sinusoidal nature and glycocalyx; contribute to the production of the GBM
  3. Visceral epithelium (podocytes)
     - one of the cells of the glomerular filtration barrier; help form the plasma filtration apparatus due to their interdigitated foot process that form slit diaphragms; contribute to the production of the GBM
  4. Parietal epithelium
     - lines the interior of Bowman’s capsule and contains a podocyte progenitor population
  5. Juxtaglomerular cells
     - smooth muscle cells in lining of afferent arteriole; produce, store and secrete renin
The Renal Tubules

- Reabsorption and secretion occur between the renal tubules and vasa recta forming urine for excretion.
- Each segment of the tubule selectively transports various solutes and water and is targeted by specific diuretics.

**Figure 1. The glomerulus**

**Renal Hemodynamic Parameters**

- RBF = 20% of CO, ~1 L/min
- RPF = RBF*(1-Hct)
- GFR = ~120 mL/min in healthy adult
  (99% of this volume is reabsorbed)
- FF = GFR/RPF (normally 20%)

**Figure 2. Tubular segments of the nephron**

- Avoid NSAIDs in patients with diarrhea, heart failure, or renal failure.
Renal Hemodynamics

- **GFR**
  - the rate of fluid transfer between glomerular capillaries and Bowman’s space
  - 180 L/d, of which 99% is reabsorbed, giving a daily urine output of 1.0-1.5 L
  - normal urine output is 0.5-2.0 ml/kg/h in adults
  - GFR is highest in early adulthood, and decreases thereafter

- **renal autoregulation** maintains constant GFR over mean arterial pressures of 70-180 mmHg

- 2 mechanisms of autoregulation
  - myogenic mechanism: release of vasoactive factors in response to changes in perfusion pressure (e.g. ↑ perfusion pressure → afferent arteriolar constriction → ↓ GFR)
  - tubuloglomerular feedback: changes in Na+ delivery to macula densa lead to changes in afferent arteriolar tone (e.g. increased delivery causes afferent constriction)

- **FF**
  - percentage of RPF filtered across the glomeruli
  - expressed as a ratio: FF = GFR/RPF; normal = 0.2 or 20%

- angiotensin II constricts renal efferent arterioles which increases FF, thereby maintaining GFR

- renin is released from juxtaglomerular apparatus in response to decreased RPF

---

**Figure 3. Renin-angiotensin-aldosterone system**

**Assessment of Renal Function**

**Measurement of Renal Function**

- **GFR** = rate of filtration of plasma by the glomeruli
- most renal functions decline in parallel with a decrease in GFR
- inulin clearance is the gold standard for measuring GFR, but very rarely used clinically
- clinically, GFR is estimated using serum creatinine concentration, [Cr]
- Cr is a metabolite of creatine (intermediate in muscle energy metabolism)
- Cr is freely filtered at the glomerulus with no tubular reabsorption
- tubular secretion varies based on level of renal function (10% to >50%)
- increased muscle mass increases rate of production of Cr
- Cr filtered = Cr excreted (at steady state)

**Ways to Estimate GFR Using Serum Creatinine Concentration**

1. **Measure CrCl**
   - calculation provides reasonable estimate of GFR
   - measure plasma [Cr], 24 h urine volume, and urine [Cr]
   - GFR/d = ([urine [Cr] x urine volume]/d)/(plasma [Cr])
   - must use same units for urine [Cr] and plasma [Cr]

2. **Estimate CrCl using Cockcroft-Gault formula**
   - serum Cr used along with age, gender, and weight (kg) to estimate GFR
   - normal range is >90 mL/min (>1.5 mL/s)

**Cockcroft-Gault Formula**

\[
\text{CrCl (mL/min)} = \frac{(weight \text{ in kg} \times 1.23 \times [Cr]_{\text{plasma}})}{(140 \text{ age} - weight \text{ in kg})} \times 0.85 \text{ for females}
\]
3. Estimate GFR using MDRD formula
   - most common way in which GFR is estimated (MDRD 7 equation)
     - complex formula incorporating age, gender, serum Cr, and African descent, but does not
       include weight
     - GFR is reported as mL/min/1.73 m² body surface area

4. Estimate GFR using CKD-EPI equation
   - the best current equation
     - calculated using serum Cr, age, sex, and race

Limitations of Using Serum Cr Measurements
1. must be in steady state
   - constant GFR and rate of production of Cr from muscles
   - sudden injury may reduce GFR substantially, but it takes time for Cr to accumulate and then
     re-establish steady state
   - clinical correlation: in AKI, the rise in Cr is often delayed
2. GFR must fall substantially before plasma [Cr] rises above normal laboratory range
   - with progressive renal failure, remaining nephrons compensate with hyperfiltration
   - GFR is relatively preserved despite significant structural damage
3. plasma [Cr] is influenced by the rate of Cr production
   - lower production with smaller muscle mass (e.g. female, elderly, low weight)
     - for example, consider plasma [Cr] of 100 µmol/L in both of these patients
       - 20 yr old man who weighs 100 kg, GFR = 144 mL/min
       - 80 yr old woman who weighs 50 kg, GFR = 30.6 mL/min
     - clinical correlation: GFR decreases with age and would not be reflected as a rise in serum Cr
       due to the age-associated decline in muscle mass
4. tubular secretion of Cr increases as GFR decreases
   - serum Cr and CrCl overestimate low GFR
   - certain drugs (cimetidine, trimethoprim) interfere with Cr secretion
5. errors in Cr measurement
   - very high bilirubin level causes [Cr] to be falsely low
   - acetocetate (a ketone body) and certain drugs (cefoxitin) create falsely high [Cr]

Measurement of Urea Concentration
- urea is the major end-product of protein metabolism
- plasma urea concentration reflects renal function but should not be used alone as it is modified
  by a variety of other factors
- urea production reflects dietary intake of protein and catabolic rate; increased protein intake or
  catabolism (sepsis, trauma, GI bleed) causes urea level to rise
- ECF volume depletion causes a rise in urea independent of GFR or plasma [Cr]
- in addition to filtration, a significant amount of urea is reabsorbed along the tubule
- reabsorption is increased in hypernatremic states such as ECF volume depletion
- typical ratio of urea to [Cr] in serum is 1:12 in SI units (using mmol/L for urea and µmol/L for Cr)

Urinalysis
- use dipstick in freshly voided urine specimen to assess the following:

1. Specific Gravity
   - ratio of the mass of equal volumes of urine/H₂O
   - range is 1.001 to 1.030
   - values <1.010 reflect dilute urine, values >1.020 reflect concentrated urine
   - value usually 1.010 in ESRD (isosthenuria: same specific gravity as plasma)

2. pH
   - urine pH is normally between 4.5-7.0; if persistently alkaline, consider
     - RA
     - UTI with urease-producing bacteria (e.g. Proteus)

3. Glucose
   - freely filtered at glomerulus and reabsorbed in proximal tubule
   - causes of glucosuria include
     1. hyperglycemia >9.11 mmol/L leads to filtration that exceeds tubular resorption capacity
     2. increased GFR (e.g. pregnancy)
     3. proximal tubule dysfunction (e.g. Fanconi’s syndrome)

4. Protein
   - dipstick only detects albumin; other proteins (e.g. Bence-Jones, Ig, Tamm-Horsfall) may be missed
   - microalbuminuria (defined as ≥2.0 mg/mmol Cr in males and ≥2.8 mg/mmol Cr in females) is
     not detected by standard dipstick (see Diabetes, NP28)
   - sulfosalicylic acid detects all protein in urine by precipitation
   - gold standard: 24 h timed urine collection for total protein
5. Leukocyte Esterase
- enzyme found in WBC and detected by dipstick
- presence of WBCs indicates infection (e.g. UTI) or inflammation (e.g. AIN)

6. Nitrites
- nitrates in urine are converted by some bacteria to nitrites
- high specificity, low sensitivity for UTI

7. Ketones
- positive in alcoholic/diabetic ketoacidosis, prolonged starvation, fasting

8. Hemoglobin
- positive in hemoglobinuria (hemolysis), myoglobinuria (rhabdomyolysis), and true hematuria (RBCs seen on microscopy)

### Urine Microscopy
- centrifuge urine specimen for 3-5 min, discard supernatant, resuspend sediment and plate on slide
- shaking tube vigorously may disrupt casts

<table>
<thead>
<tr>
<th>Table 2. Comparison of Urinary Sediment Findings</th>
</tr>
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<tbody>
<tr>
<td><strong>Active Sediment</strong> = Suggestive of Parenchymal Kidney Disease</td>
</tr>
<tr>
<td>-------------------------------------------------</td>
</tr>
<tr>
<td>Any one or more of the following seen on microscopy</td>
</tr>
<tr>
<td>Red cell casts</td>
</tr>
<tr>
<td>White cell casts</td>
</tr>
<tr>
<td>Muddy-brown granular or epithelial cell casts</td>
</tr>
<tr>
<td>&gt;2 red cells per HPF</td>
</tr>
<tr>
<td>&gt;4 white cells per HPF</td>
</tr>
</tbody>
</table>

1. CELLS

**Erythrocytes**
- normal range = up to 2-3 RBCs per HPF
- hematuria = greater than 2-3 RBCs per HPF
- dysmorphic RBCs and/or RBC casts suggest glomerular bleeding (e.g. proliferative GN)
- isomorphic RBCs, no casts suggest extraglomerular bleeding (e.g. bladder Ca)

**Leukocytes**
- normal range = up to 3 WBCs per HPF
- pyuria = greater than 3 WBCs per HPF
- indicates inflammation or infection
- if persistent sterile pyuria present (i.e. negative culture), consider: chronic urethritis, prostatitis, interstitial nephritis, calculi, papillary necrosis, renal TB, viral infections

**Eosinophils**
- detected using Wright’s or Hansel’s stain (not affected by urine pH)
- consider AIN, atheroembolic disease

**Oval Fat Bodies**
- renal tubular cells filled with lipid droplets
- seen in heavy proteinuria (e.g. nephrotic syndrome)

2. CASTS
- cylindrical structures formed by intratubular precipitation of Tamm-Horsfall mucoprotein; cells may be trapped within the matrix of protein

<table>
<thead>
<tr>
<th>Table 3. Interpretation of Casts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Casts</strong></td>
</tr>
<tr>
<td>---------------------------------</td>
</tr>
<tr>
<td>Hyaline casts</td>
</tr>
<tr>
<td>RBC casts</td>
</tr>
<tr>
<td>WBC casts</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Pigmented granular casts</td>
</tr>
<tr>
<td>(heme granular casts, muddy brown)</td>
</tr>
<tr>
<td>Fatty casts</td>
</tr>
</tbody>
</table>
3. CRYSTALS
- uric acid: consider acid urine, hyperuricosuria
- calcium phosphate: alkaline urine
- calcium oxalate: consider hyperoxaluria, ethylene glycol poisoning
- sulfur: sulfa-containing antibiotics

**Urine Biochemistry**
- commonly measure: Na⁺, K⁺, Cl⁻, osmolality, and pH
- no "normal" values; electrolyte excretion depends on intake and current physiological state
- results must be interpreted in the context of a patient's current state, for example:
  1. ECF volume depletion: expect low urine [Na⁺] (kidneys should be retaining Na⁺)
     - i.e. high urine [Na⁺] (>40 mmol/L) in the setting of AKI: suggests renal disease
     - i.e. high urine [Na⁺] (>40 mmol/L) in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter's syndrome), SIADH
  - urine [Na⁺] <20 mmol/L suggests a prerenal problem
  - i.e. high urine [Na⁺] (>40 mmol/L) in the setting of AKI: suggests renal disease
  - i.e. high urine [Na⁺] (>40 mmol/L) in the setting of hyponatremia: generally from causes such as diuretics, tubular disease (e.g. Bartter's syndrome), SIADH
  2. daily urinary potassium excretion rate should be decreased (<20 mmol/d) in hypokalemia
     - if higher than 20 mmol/d, suggests renal contribution to hypokalemia
  - osmolality is useful to estimate the kidney's concentrating ability
  - FENa refers to the fractional excretion of Na⁺
  - FEₙa = urine [Na⁺] x plasma [Cr] / (plasma [Na⁺] x urine [Cr])
  - FEₙa <1% suggests the pathology is prerenal
  - urine pH is useful to grossly assess renal acidification
  - a low pH (<5.5) in the presence of low serum pH is an appropriate renal response
  - a high pH in this setting might indicate a renal acidification defect (e.g. RTA)

**Electrolyte Disorders**

### Sodium Homeostasis
- hyponatremia and hypernatremia are disorders of water balance
- hyponatremia usually suggests too much water in the ECF relative to Na⁺ content
- hypernatremia usually suggests too little water in the ECF relative to Na⁺ content
- solutes (such as Na⁺, K⁺, glucose) that cannot freely traverse the plasma membrane contribute to effective osmolality and induce transcellular shifts of water
- water moves out of cells in response to increased ECF osmolality
- water moves into cells in response to decreased ECF osmolality
- ECF volume is determined by Na⁺ content rather than concentration
- Na⁺ deficiency leads to ECF volume contraction
- Na⁺ excess leads to ECF volume expansion
- clinical signs and symptoms of hyponatremia and hypernatremia are secondary to cells (especially in the brain) shrinking (hyponatremia) or swelling (hyponatremia)

<table>
<thead>
<tr>
<th>Table 4. Clinical Assessment of ECF Volume (Total Body Na⁺)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluid Compartment</strong></td>
</tr>
<tr>
<td>Intravascular</td>
</tr>
<tr>
<td>JVP</td>
</tr>
<tr>
<td>Blood pressure</td>
</tr>
<tr>
<td>Auscultation of heart</td>
</tr>
<tr>
<td>Auscultation of lungs</td>
</tr>
<tr>
<td>Interstitial</td>
</tr>
<tr>
<td>Skin turgor</td>
</tr>
<tr>
<td>Edema (dependent)</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Urine output</td>
</tr>
<tr>
<td>Body weight</td>
</tr>
<tr>
<td>Hematocrit, serum protein</td>
</tr>
</tbody>
</table>

*If there is a renal abnormality (e.g. osmotic diuresis), the urine output may be increased despite the presence of hypovolemia
Hyponatremia

Hyponatremia: serum [Na⁺] < 135 mmol/L
- can be associated with hypo-osmolality (most common), iso-osmolality, or hyperosmolality
- consider if it is “appropriate” vs. “inappropriate” ADH secretion
- if appropriate ADH secretion, is it real vs. effective volume loss?

Signs and Symptoms
- depend on degree of hyponatremia and more importantly, velocity of progression from onset
- hyponatremia = swollen cells
- acute hyponatremia (<24-48 h) more likely to be symptomatic
- chronic hyponatremia (>24-48 h) less likely to be symptomatic due to adaptation
  - adaptation: normalization of brain volume through loss of cellular electrolytes (within hours) and organic osmolytes (within days)
  - adaptation is responsible for the risks associated with overly rapid correction
- neurologic symptoms predominate (secondary to cerebral edema): headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, disorientation, personality changes, depressed reflexes, decreased LOC

Complications
- seizures, coma, respiratory arrest, permanent brain damage, brainstem herniation, death
- risk of brain cell shrinkage with rapid correction of hyponatremia
  - can develop osmotic demyelination of pontine and extrapontine neurons; may be irreversible (e.g. central pontine myelinolysis: cranial nerve palsies, quadriplegia, decreased LOC)

Risk Factors for Osmotic Demyelination
- rise in serum [Na⁺] with correction > 8 mmol/L/d if chronic hyponatremia
- associated hypokalemia and/or malnutrition (e.g. low muscle mass)
- if patient with hyponatremia and hypovolemia is given large volume of isotonic fluid (ADH is stimulated by hypovolemia); when hypovolemia is corrected, the ADH level falls suddenly causing sudden brisk water diuresis, and therefore rapid rise in serum Na⁺ level
- patient with psychogenic polydipsia, deprived of water

Investigations
- ECF volume status assessment (see Table 4)
- serum electrolytes, glucose, Cr
- serum osmolality, urine osmolality
- urine Na⁺ (urine Na⁺ < 10-20 mmol/L suggests volume depletion as the cause of hyponatremia)
- assess for causes of SIADH (see Table 5)
- TSH, free T4, and cortisol levels
- consider CXR and possibly CT chest if suspect pulmonary cause of SIADH (e.g. small cell lung cancer)
- consider CT head if suspect CNS cause of SIADH
Treatment of Hyponatremia
- general measures for all patients
  1) treat underlying cause (e.g. restore ECF volume if volume depleted, remove offending drug, treat pain, nausea, etc.)
  2) restrict free water intake
  3) promote free water loss
  4) carefully monitor serum Na⁺, urine volume, and urine tonicity
  5) ensure frequently that correction is not occurring too rapidly
    - monitor urine output frequently: high output of dilute urine is the first sign of dangerously rapid correction of hyponatremia

A. Known Acute (known to have developed over <24-48 h)
- commonly occurs in hospital (dilute IV fluid, post-operative increased ADH)
- less risk from rapid correction since adaptation has not fully occurred
- if symptomatic
  - correct rapidly with 3% NaCl 1-2 cc/kg/h up to serum [Na⁺] = 125-130 mmol/L
  - may need furosemide to address volume overload
- if asymptomatic, treatment depends on severity
  - if marked fall in plasma [Na⁺], treat as symptomatic

B. Chronic or Unknown
1. if severe symptoms (seizures or decreased LOC)
   - must partially correct acutely
   - aim for increase of Na⁺ by 1-2 mmol/L/h for 4-6 h
   - limit total rise to 8 mmol/L in 24 h
   - IV 3% NaCl at 1-2 cc/kg/h
   - may need furosemide
2. if asymptomatic
   - water restrict to <1 L/d fluid intake
   - consider IV 0.9% NS + furosemide (reduces urine osmolality, augments excretion of H₂O)
   - consider NaCl tablet or Oxocubes as a source of Na⁺
3. refractory
   - furosemide and oral salt tablets
   - oral urea (osmotic aquarexis)
   - V₂ receptor antagonists (e.g. tolvaptan)
4. always pay attention to patient’s ECF volume status – if already volume-expanded, unlikely to give NaCl; if already volume-depleted, almost never appropriate to give furosemide

C. Options for Treatment of Overly-Rapid Correction
- give water (IV D5W)
- give ADH to stop water diuresis (DDAVP 1-2 µg IV)

Impact of IV Solution on Serum [Na⁺]
- formula to estimate the change in serum [Na⁺] caused by retention of 1 L of any infusate
  \[
  \text{change in serum [Na⁺]} = \frac{\text{infusate [Na⁺]} - \text{serum [Na⁺]}}{\text{TBW} + 1 \text{ L}}
  \]
- formula assumes there are no losses of water or electrolytes

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION
1. urine that is inappropriately concentrated for the serum osmolality
2. high urine sodium (>20-40 mmol/L)
3. high FÉ₆₆
Table 5. Disorders Associated with SIADH

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Pulmonary</th>
<th>CNS</th>
<th>Drugs</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small cell cancer</td>
<td>Pneumonia</td>
<td>Mass lesion</td>
<td>Antidepressants</td>
<td>Post-operative state</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>Lung abscess</td>
<td>Encephalitis</td>
<td>TCAs</td>
<td>Pain</td>
</tr>
<tr>
<td>Pancreatic adenocarcinoma</td>
<td>TB</td>
<td>Subarachnoid hemorrhage</td>
<td>SSRI</td>
<td>Severe nausea</td>
</tr>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>Acute respiratory failure</td>
<td>Stroke</td>
<td>Antineoplastics</td>
<td>HIV</td>
</tr>
<tr>
<td>Thymoma</td>
<td>Asthma</td>
<td>Head trauma</td>
<td>Vincristine</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>COPD</td>
<td>Acute psychosis</td>
<td>Cyclophosphamide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Positive pressure ventilation</td>
<td>Acute intermittent porphyria</td>
<td>Barbiturates</td>
<td></td>
</tr>
</tbody>
</table>

Hypernatremia

- hypernatremia: serum [Na⁺] >145 mmol/L
- too little water relative to total body Na⁺; always a hyperosmolar state
- usually due to NET water loss, rarely due to hypertonic Na⁺ gain
- less common than hyponatremia because patients are protected against hypernatremia by thirst and release of ADH

Signs and Symptoms
- with acute hypernatremia no time for adaptation, therefore more likely to be symptomatic
- adaptive response: cells import and generate new osmotically active particles to normalize size
- due to brain cell shrinkage: altered mental status, weakness, neuromuscular irritability, focal neurologic deficits, seizures, coma, death
- ± polyuria, thirst, signs of hypovolemia

Complications
- increased risk of vascular rupture resulting in intracranial hemorrhage
- rapid correction may lead to cerebral edema due to ongoing brain hyperosmolality

Treatment of Hypernatremia
- general measures for all patients
  - give free water (oral or IV)
  - treat underlying cause
  - monitor serum Na⁺ frequently to ensure correction is not occurring too rapidly
- if evidence of hemodynamic instability, must first correct volume depletion with NS bolus
- loss of water is often accompanied by loss of Na⁺, but a proportionately larger water loss
- use formula to calculate free water H₂O deficit and replace
- encourage patient to drink pure water, as oral route is preferred for fluid administration
- if unable to replace PO or NG, correct H₂O deficit with hypotonic IV solution (IV D5W, 0.45% NS [half normal saline], or 3.3% dextrose with 0.3% NaCl [“2/3 and 1/3”])
- use formula (see Hypernatremia, NP8) to estimate expected change in serum Na⁺ with 1 L infusate
- aim to lower [Na⁺] by no more than 12 mmol/L in 24 h (0.5 mmol/L/h)
- must also provide maintenance fluids and replace ongoing losses
- general rule: give 2 cc/kg/h of free water to correct serum [Na⁺] by about 0.5 mmol/L/h or 12 mmol/L/d

H₂O Deficit and TBW Equations
- TBW = 0.6 x wt (kg) men
- TBW = 0.5 x wt (kg) women
- H₂O deficit = TBW x ([Na⁺]plasma – 140) / 140

Correction of serum [Na⁺] in hypernatremia should not exceed 12 mmol/L/24 h

1 L D5W approximately equals 1 L of free water
1 L 0.45% NS approximately equals 500 mL of free water
DIABETES INSIPIDUS

- collecting tubule is impermeable to water due to absence of ADH or impaired response to ADH
- defect in central release of ADH (central DI) or renal response to ADH (nephrogenic DI)

Etiology

- central DI: neurosurgery, granulomatous diseases, trauma, vascular events, and malignancy
- nephrogenic DI: lithium (most common), hypokalemia, hypercalcemia, and congenital

Diagnosis

- urine osmolality inappropriately low in patient with hypernatremia (Uosm <300 mOsm/kg)
- serum vasopressin concentration may be absent or low (central), or elevated (nephrogenic)
- dehydration test: H2O deprivation until loss of 3% of body weight or until urine osmolality rises above plasma osmolality; if urine osmolality remains <300 (fails to concentrate urine), most likely DI
- administer DDAVP (exogenous ADH) (10 µg intranasally or 2 µg SC or IV)
  • central DI: diagnosed if there is rise in urine osmolality, fall in urine volume
  • treat with DDAVP
  • nephrogenic DI: exogenous ADH fails to concentrate urine as kidneys do not respond
  • treat with water (IV D5W or PO water), thiazides may help as well (reduced ECF volume stimulates proximal tubular reabsorption of sodium and water, leading to less delivery of glomerular filtrate to ADH sensitive parts of renal tubule, and therefore lower urine volume results)

Potassium Homeostasis

- approximately 98% of total body K⁺ stores are intracellular
- normal serum K⁺ ranges from 3.5-5.0 mEq/L
- in response to K⁺ load, rapid removal from ECF is necessary to prevent life-threatening hyperkalemia
- insulin, catecholamines, and acid-base status influence K⁺ movement into cells
  • aldosterone has a minor effect
- potassium excretion is regulated at the distal nephron
  • K⁺ excretion = urine flow rate x urine [K⁺]

Factors which Increase Renal K⁺ Loss

- hyperkalemia
- increased distal tubular urine flow rate and Na⁺ delivery (thiazides and loop diuretics)
- increased aldosterone activates epithelial sodium channels in cortical collecting duct, causing Na⁺ reabsorption and K⁺ excretion
- metabolic alkalosis (increases K⁺ secretion)
- hypomagnesemia
- increased non-reabsorbable anions in tubule lumen: HCO₃⁻, penicillin, salicylate (increased tubular flow rate increases K⁺ secretion)

Hypokalemia

- serum [K⁺] <3.5 mEq/L

Signs and Symptoms

- usually asymptomatic, particularly when mild (3.0-3.5 mmol/L)
- N/V, fatigue, generalized weakness, myalgia, muscle cramps, and constipation
- if severe: arrhythmias, muscle necrosis, and rarely paralysis with eventual respiratory impairment
- arrhythmias occur at variable levels of K⁺; more likely if digoxin use, hypomagnesemia, or CAD
- ECG changes are more predictive of clinical picture than serum [K⁺]
  • U waves most important (low amplitude wave following a T wave)
  • flattened or inverted T waves
  • depressed ST segment
  • prolongation of Q-T interval
  • with severe hypokalemia: P-R prolongation, wide QRS, arrhythmias; increases risk of digitalis toxicity

Figure 6. ECG changes in hypokalemia
### Approach to Hypokalemia

1. **emergency measures:** obtain ECG; if potentially life threatening, begin treatment immediately
2. rule out transcellular shifts of K⁺ as cause of hypokalemia
3. assess contribution of dietary K⁺ intake
4. spot urine K:Cr (should be less than 1 in setting of hypokalemia)
   - if <1 consider GI loss
   - if >1 consider a renal loss
5. consider 24 h K⁺ excretion
6. if renal K⁺ loss, check BP and acid-base status
7. may also assess plasma renin and aldosterone levels, serum [Mg²⁺]

---

### Treatment

- **treat underlying cause**
- if true K⁺ deficit, potassium repletion (decrease in serum [K⁺] of 1 mEq is roughly 100-200 mEq of total body loss)
  - oral sources – food, tablets (K-Dur™), KCl liquid solutions (preferable route if the patient tolerates PO medications)
  - IV – usually KCl in saline solutions, avoid dextrose solutions (may exacerbate hypokalemia via insulin release)
    - max 40 mmol/L via peripheral vein, 60 mmol/L via central vein, max infusion 20 mmol/h
  - K⁺-sparring diuretics (triangularerene, spironolactone, amiloride) can prevent renal K⁺ loss
- restore Mg²⁺ if necessary
- if urine output and renal function are impaired, correct with extreme caution
- risk of hyperkalemia with potassium replacement especially high in elderly, diabetics, and patients with decreased renal function
- beware of excessive potassium repletion, especially if transcellular shift caused hypokalemia

---

### Hyperkalemia

- **serum [K⁺] >5.0 mEq/L**

### Signs and Symptoms

- usually asymptomatic but may develop nausea, palpitations, muscle weakness, muscle stiffness, paresthesias, areflexia, ascending paralysis, and hypoventilation
- impaired renal ammoniagenesis and metabolic acidosis
• ECG changes and cardiotoxicity (do not correlate well with serum [K⁺])
  ▪ peaked and narrow T waves
  ▪ decreased amplitude and eventual loss of P waves
  ▪ prolonged PR interval
  ▪ widening of QRS and eventual merging with T wave (sine-wave pattern)
  ▪ AV block
  ▪ ventricular fibrillation, asystole

![ECG changes in hyperkalemia](image)

**Figure 8. ECG changes in hyperkalemia**

**Table 6. Causes of Hyperkalemia**

<table>
<thead>
<tr>
<th>Factitious</th>
<th>Increased Intake</th>
<th>Transcellular Shift</th>
<th>Decreased Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample hemolysis*</td>
<td>Diet</td>
<td>Intravascular hemolysis</td>
<td>Decreased GFR</td>
</tr>
<tr>
<td>Sample taken from vein where IV KCl is running</td>
<td>KCl tabs</td>
<td>Rhabdomyolysis</td>
<td>• Renal failure</td>
</tr>
<tr>
<td>Prolonged use of tourniquet</td>
<td>IV KCl</td>
<td>Tumour lysis syndrome</td>
<td>• Low effective circulating volume</td>
</tr>
<tr>
<td>Leukocytosis (extreme)</td>
<td>Salt substitute</td>
<td>Insulin deficiency</td>
<td>• NSAIDs in renal insufficiency</td>
</tr>
<tr>
<td>Thrombocytosis (extreme)</td>
<td></td>
<td>Acidemia</td>
<td>Normal GFR but hypoaldosteronism</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td>Drugs</td>
<td></td>
</tr>
<tr>
<td>KCl tabs</td>
<td></td>
<td>• β-blockers</td>
<td></td>
</tr>
<tr>
<td>IV KCl</td>
<td></td>
<td>• Digitalis overdose (blocks Na⁺/K⁺ ATPase)</td>
<td></td>
</tr>
<tr>
<td>Salt substitute</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Most common

**Table 7. Causes of Hyperkalemia with Normal GFR**

<table>
<thead>
<tr>
<th>Decreased Aldosterone Stimulus (low renin, low aldosterone)</th>
<th>Decreased Aldosterone Production (normal renin, low aldosterone)</th>
<th>Aldosterone Resistance (decreased tubular response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Associated with diabetic nephropathy, NSAIDs, chronic interstitial nephritis, HIV</td>
<td>• Adrenal insufficiency of any cause (e.g. Addison’s disease, AIDS, metastatic cancer)</td>
<td>K⁺-sparing drugs</td>
</tr>
<tr>
<td></td>
<td>• ACEI</td>
<td>• Spironolactone</td>
</tr>
<tr>
<td></td>
<td>• Angiotensin II receptor blockers</td>
<td>• Amiloride</td>
</tr>
<tr>
<td></td>
<td>• Heparin</td>
<td>• Triamterene</td>
</tr>
<tr>
<td></td>
<td>• Congenital adrenal hyperplasia with 21-hydroxylase deficiency</td>
<td>Renal tubulointerstitial disease</td>
</tr>
</tbody>
</table>

**Approach to Hyperkalemia**
1. emergency measures: obtain ECG, if life threatening begin treatment immediately
2. rule out factitious hyperkalemia; repeat blood test
3. hold exogenous K⁺ (PO and IV) and any K⁺ retaining medications
4. assess potential causes of transcellular shift
5. estimate GFR (calculate CrCl using Cockcroft-Gault)

**Treatment**
- acute therapy is warranted if ECG changes are present or if patient is symptomatic
- tailor therapy to severity of increase in [K⁺] and ECG changes
  - [K⁺] <6.5 and normal ECG
    - treat underlying cause, stop K⁺ intake, increase the loss of K⁺ via urine and/or GI tract
  - [K⁺] between 6.5 and 7.0, no ECG changes: add insulin to above regimen
  - [K⁺] >7.0 and/or ECG changes: first priority is to protect the heart, add calcium gluconate to above

1. **Protect the Heart**
- calcium gluconate 1-2 amps (10 mL of 10% solution) IV
- antagonizes cardiac toxicity of hyperkalemia, protects cardiac conduction system, no effect on serum [K⁺]
- onset within minutes, lasts 30-60 min (may require repeat doses during treatment course of hyperkalemia)
2. Shift K⁺ into Cells
• regular insulin (Insulin R) 10-20 units IV, with 1-2 amp D50W (give D50W before insulin)
  ▪ onset of action 15-30 min, lasts 1-2 h
  ▪ monitor capillary blood glucose q1h because of risk of hypoglycemia
  ▪ can repeat every 4-6 h
  ▪ caution giving D50W before insulin if hyperkalemia is severe as it can cause a serious arrhythmia
• NaHCO₃ 1-3 ampules (given as 3 ampules of 7.5% or 8.4% NaHCO₃ in 1L D5W)
  ▪ onset of action 15-30 min, transient effect, drives K⁺ into cells in exchange for H⁺
  ▪ more effective if patient has metabolic acidosis
• β₂-agonist (Ventolin*) in nebulized form (dose = 2 cc or 10 mg inhaled) or 0.5 mg IV
  ▪ onset of action 30-90 min, stimulates Na⁺/K⁺ ATPase
  ▪ caution if patient has heart disease as may result in tachycardia

3. Enhance K⁺ Removal from Body
• via urine (preferred approach)
  ▪ furosemide (≥40 mg IV), may need IV NS to avoid hypovolemia
  ▪ fludrocortisone (synthetic mineralocorticoid) if suspect aldosterone deficiency
• via gastrointestinal tract
  ▪ cation-exchange resins: calcium resinium or sodium polystyrene sulfonate (Kayexalate*)
    ▪ increasingly falling out of favour due to risk of colonic necrosis; works by binding Na⁺ in exchange for K⁺, and controversial how much K⁺ is actually removed
    ▪ lactulose PO to avoid constipation (must ensure that patient has a bowel movement after resin is administered - main benefit may be the diarrhea caused by lactulose)
  ▪ Kayexalate* enemas with tap water
• dialysis (renal failure, life threatening hyperkalemia unresponsive to therapy)

---

**Acid-Base Disorders**

- acid-base homeostasis influences protein function and can critically affect tissue and organ function with consequences to cardiovascular, respiratory, metabolic, and CNS function
- see Respiratory, R6 for more information on respiratory acidosis/alkalosis
- normal concentration of HCO₃⁻ = 24 mEq/L (range: 22-30 mEq/L)
- normal pCO₂ = 40 mmHg (range: 36-44 mmHg)
- each acid base disorder has an appropriate compensation
  - inadequate compensation or overcompensation can indicate the presence of a second acid-base disorder (e.g. in metabolic acidosis, inadequate compensation means there is also respiratory acidosis; overcompensation means there is also respiratory alkalosis)

---

**Figure 9. Approach to acid-base disorders**
**Approach**

1. **Identify the primary disturbance** (see Figure 9)
   - respiratory acidosis, metabolic acidosis, respiratory alkalosis, metabolic alkalosis

2. **Evaluate compensation. If compensation is not appropriate, a second acid-base disorder is likely present**
   - compensation occurs in the same direction as the primary disturbance

3. **Calculate Plasma AG**
   - \[ AG = [Na^+] - ([HCO_3^-] + [Cl^-]) \]
   - baseline = 12, range 10-14 mEq/L
   - AG can be altered by plasma albumin level: for each 10 g/L fall in albumin, lower baseline AG by 3 mEq/L (e.g. if plasma [albumin] = 20 g/L, expect AG = 6 mEq/L)

4. **If AG elevated, compare increase in AG with decrease in HCO_3^-**
   - if increase in AG < decrease in HCO_3^-, there is a coexisting non-AG metabolic acidosis
   - if increase in AG > decrease HCO_3^-, there is a coexisting metabolic alkalosis

5. **Calculate Osmolar Gap**
   - osmolar gap = measured osmolality – calculated osmolality
   - calculated osmolality = (2 x [Na^+]) + [urea] + [glucose] (all units are in mmol/L)
   - normal osmolar gap <10
   - if AG >10, consider: methanol poisoning, ethylene glycol poisoning, or another cause of acidosis plus ethanol ingestion

---

**Metabolic Acidosis**

**Etiology and Pathophysiology**

1. **Increased AG Metabolic Acidosis (4 types)**
   1. Lactic acidosis (2 types)
      - L-lactic acid
        - Type A: due to tissue hypoperfusion (any cause of shock), ischemic bowel, profound hypoxemia
        - Type B: non-hypoxic – multiple causes; the most common is failure to metabolize normally produced lactic acid in the liver due to severe liver disease; other causes include: excessive alcohol intake, thiamine deficiency, metformin accumulation (metformin interferes with electron transport chain), certain anti-retrovirals, large tumours, mitochondrial myopathies
      - D-lactic acid: rare syndrome characterized by episodes of encephalopathy and metabolic acidosis
        - occurs in the setting of carbohydrate malabsorption (e.g. short bowel syndrome), colonic bacteria metabolize carbohydrate load into D-lactic acid, diminished colonic motility and impaired D-lactate metabolism
   2. Ketoacidosis
      - diabetic
        - starvation
      - alcoholic (decreased carbohydrate intake and vomiting)
   3. Toxins
      - methanol (toxic to brain and retina, can cause blindness and brain death): metabolized to formic acid
      - ethylene glycol (toxic to brain and kidneys): metabolized to oxalic acid (envelope shaped crystals in urine) and multiple other acids
      - salicylate (e.g. ASA) overdose: causes acidosis due to salicylic acid, and also accumulation of lactic acid (salicylate at toxic levels impairs electron transport chain) and ketoacidosis (salicylate activates fat breakdown)
   4. Advanced renal failure (e.g. serum Cr increased at least 5x above baseline – a very low GFR causes anion retention, and renal disease leads to impaired bicarbonate production)

2. **Normal AG Metabolic Acidosis (Hyperchloremic Acidosis)**
   1. diarreha (HCO_3^- loss from GI tract)
   2. **RTA**
      - type I RTA (distal): inability to secrete H^+ in collecting duct, leading to impaired excretion of ammonium into urine
      - type II RTA (proximal): impaired HCO_3^- reabsorption
      - type III RTA: combination of Types I and II and is extremely rare
      - type IV RTA: defective ammoniagenesis due to decreased aldosterone, hyporesponsiveness to aldosterone, or hyperkalemia

---

**Causes of Increased Osmolar Gap**
- Methanol
- Ethylene glycol
- Ethanol
- Polyethylene glycol
- Mannitol
- Sorbitol

**Useful Equations**
- AG = [Na^+] - [Cl^-] - [HCO_3^-] (normal range = 10-14 mEq/L)
- Osmolar Gap = measured serum osmolality – calculated osmolality (normal <10 mEq/L)
- “Two Salts and a Sticky BUN”
- Calculated Osmolality = 2[Na^+] + [Urea] + [Glucose] +1.25[Ethanol]

**Causes of Increased AG Metabolic Acidosis**
- **MUDPILES CAT**
  - Methanol
  - Uremia
  - Diabetic ketoacidosis
  - Paraldehyde
  - Isopropyl alcohol/isonicotinamide
  - Indomethacin
  - Lactic acidosis
  - Ethylene glycol
  - Salicylates
  - Cyanide and Carbon monoxide
  - Alcoholic ketoacidosis
  - Toluene
  - or

**KARMEL**
- Ketoacidosis
- ASA
- Renal failure
- Methanol
- Ethylene glycol
- Lactic acidosis

**Causes of Non-AG Metabolic Acidosis**
- **HARDUP**
  - Hyperalimentation
  - Acetazolamide
  - RTA*
  - Diarrhea*
  - Ureteroenteric fistula
  - Pancreaticoduodenal fistula
- *Most common
• to help distinguish renal causes from non-renal causes, use Urine AG = (Na⁺ + K⁺) – Cl⁻  
  - calculation establishes the presence or absence of unmeasured positive ions (e.g. NH₄⁺) in urine  
    - if UAG < 0, suggests adequate NH₄⁺ excretion in urine (likely nonrenal cause: diarrhea)  
    - if UAG > 0, suggests problem is lack of NH₄⁺ in urine (e.g. distal RTA)

**Treatment of Metabolic Acidosis**
1. treat underlying cause  
   - fluid resuscitation insulin for DKA  
   - restore tissue perfusion for Type A lactic acidosis  
   - ethanol/fomepizole +/- dialysis for methanol or ethylene glycol poisoning  
   - alkaline diuresis ± dialysis if ASA overdose
2. correct coexisting disorders of K⁺ (see *Hyperkalemia*, NP13)
3. consider treatment with exogenous alkali (e.g. NaHCO₃) if  
   - severe reduction in [HCO₃⁻] e.g. < 8 mmol/L, especially with very low pH (< 7)  
   - no metabolizable anion (e.g. salicylate, formate, oxalate, or sulphate); note that lactate and ketoacid anions can be metabolized to HCO₃⁻  
   - note: risks of sodium bicarbonate therapy  
     - hypokalemia: causes K⁺ to shift into cells (correct K⁺ deficit first)  
     - ECF volume overload: Na⁺ load given with NaHCO₃, can exacerbate pulmonary edema  
     - overshoot alkalosis: abrupt, poorly tolerated transition from overly aggressive alkali loading, partial conversion of accumulated organic anions to HCO₃⁻, and persisting hyperventilation

**Pathophysiology**
• requires initiating event and maintenance factors  
• precipitating factors  
  - GI (vomiting, NG tube) or renal loss of H⁺  
  - exogenous alkali (oral or parenteral administration), milk alkali syndrome  
  - diuretics (contraction alkalosis): decreased excretion of HCO₃⁻, decreased ECF volume, therefore increased [HCO₃⁻]  
  - post-hypercapnia: renal compensation for respiratory acidosis is HCO₃⁻ retention, rapid correction of respiratory disorder results in transient excess of HCO₃⁻  
• maintenance factors  
  - volume depletion: increased proximal reabsorption of NaHCO₃ and increased aldosterone  
  - hyperaldosteronism (1º or 2º): distal Na⁺ reabsorption in exchange for K⁺ and H⁺ excretion leads to HCO₃⁻ generation; aldosterone also promotes hypokalemia  
  - hypokalemia: transcellular K⁺/H⁺ exchange, stimulus for ammoniagenesis and HCO₃⁻ generation

**Metabolic Alkalosis**

![Metabolic alkalosis diagram](image)

**Evaluate Compensation (identify co-existing respiratory acid-base disorders)**
• hypoventilation (an upper limit to compensation exists – breathing cannot be stopped)

**Treatment**
• treat underlying cause  
• correct underlying disease, replenish K⁺ and Mg²⁺ deficits, and possibly K⁺-sparking diuretic

**3 Clinical Scenarios that Produce a Mixed Disorder with Near Normal pH**
- Cirrhosis  
- ASA overdose  
- Sepsis

**Figure 10. Approach to metabolic alkalosis**

**Note:** cannot use U₆Cl to assess volume status in presence of alkalemia:  
↑ HCO₃ excretion, drags Na → ↑ Na excretion  
U₆Cl = Urine chloride
Acute Kidney Injury

Definition
- abrupt decline in renal function leading to increased nitrogenous waste products normally excreted by the kidney
- formerly known as acute renal failure

Clinical Presentation
- azotemia (increased BUN, Cr)
- abnormal urine volume: formally <0.5 ml/kg/h for >6 h but can manifest as anuria, oliguria, or polyuria

Approach to AKI

Investigations
- blood work: CBC, electrolytes, Cr, urea (think prerenal if increase in urea is relatively greater than increase in Cr), Ca^{2+}, PO_{4}^{3-}
- urine volume, C&S, R&M: sediment, casts, crystals
- urinary indices: electrolytes, osmolality
- Foley catheterization (rule out bladder outlet obstruction)
- fluid challenge (e.g. fluid bolus to rule out most prerenal causes)
- imaging: abdomen U/S (assess kidney size, hydronephrosis, postrenal obstruction)
- indications for renal biopsy
  - diagnosis is not certain
  - prerenal azotemia or ATN is unlikely
  - oliguria persists >4 wk

Treatment
1. preliminary measures
   - prerenal
     - correct prerenal factors: optimize volume status and cardiac performance using fluids that will stay in the plasma subcompartment (NS, albumin, blood/plasma), hold ACEI/ARB (gently rehydrate when needed, e.g. CHF)
   - renal
     - address reversible renal causes: discontinue nephrotoxic drugs, treat infection, and optimize electrolytes

Clues to Prerenal Etiology
- Clinical: Decreased BP, increased HR, and orthostatic HR and BP changes
- Increased [urea] >> Increased [Cr]
- Urine [Na+] <10-20 mEq/L
- Urine [Na+] / [Cr] <20 >40
- Urine osmolality >500 <350 mOsm/kg
- Fractional excretion of Na+ <1%

Clues to Renal Etiology
- Appropriate clinical context
- Urinalysis positive for casts:
  - Pigmented granular – ATN
  - WBC – AIN
  - RBC – GN

Clues to Postrenal Etiology
- Known solitary kidney
- Older man
- Recent retroperitoneal surgery
- Anuria
- Palpable bladder
- Ultrasound shows hydronephrosis

Differentiating Prerenal from ATN

<table>
<thead>
<tr>
<th></th>
<th>Prerenal</th>
<th>ATN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinalysis</td>
<td>Normal</td>
<td>RBC, pigmented</td>
</tr>
<tr>
<td>Urine Na^+</td>
<td>&lt;20</td>
<td>&gt;40 mEq/L</td>
</tr>
<tr>
<td>Urine Na^+ / Cr</td>
<td>&lt;20</td>
<td>&gt;40</td>
</tr>
<tr>
<td>Urine osmolality</td>
<td>&gt;500</td>
<td>&lt;350 mOsm/kg H_2O</td>
</tr>
<tr>
<td>Fetta</td>
<td>&lt;1%</td>
<td>&gt;1%</td>
</tr>
</tbody>
</table>

Drugs Implicated in Prerenal Azotemia
- Diuretics
- NSAIDs
- ACEI/ARBs

Renal transplant is not a therapy for AKI
2. treat complications
   - fluid overload
     - NaCl restriction
     - high dose loop diuretics
   - hyperkalemia (see Approach to Hyperkalemia, NP12)
     - adjust dosages of medications cleared by kidney (e.g. amiodarone, digoxin, cyclosporin, tacrolimus, some antibiotics, and chemotherapeutic agents)
   - dialysis

3. definitive therapy depends on etiology

Prognosis
- high morbidity and mortality in patients with sustained AKI and multi-organ failure

Parenchymal Kidney Diseases

Glomerular Diseases

HISTOLOGICAL TERMS OF GLOMERULAR CHANGES

Extent of Changes
- histological term describing the number of glomeruli affected in a given condition:
  - diffuse: majority of glomeruli abnormal
  - focal: some glomeruli affected
- histological term describing the extent to which individual glomeruli are affected in a given condition
  - global: entire glomerulus abnormal
  - segmental: only part of the glomerulus abnormal

Types of Changes
- proliferation: hyperplasia of one of the glomerular cell types (mesangial, endothelial, parietal epithelial), with or without inflammatory cell infiltration
- membranous changes: capillary wall thickening due to immune deposits or alterations in basement membrane
- crescent formation: parietal epithelial cell proliferation and mononuclear cell infiltration form crescent-shape in Bowman's space

CLINICAL PRESENTATION OF GLOMERULAR DISEASE

Important Points to Remember
- glomerular diseases have diverse clinical presentations including hematuria, proteinuria, HTN, edema, and decreased GFR
  - each glomerulopathy presents as one of four major glomerular syndromes (these are NOT diagnoses)
    1. asymptomatic urinary abnormalities
       - proteinuria
       - hematuria
    2. nephritic syndrome
       - acute GN
       - rapidly progressive GN
    3. nephrotic syndrome
    4. ESRD

- glomerulopathies can be caused by a primary disease or can occur secondary to a systemic disease
- some glomerulopathies can present as more than one syndrome at different times

The Nephritic-Nephrotic Spectrum
- glomerular pathology can present with a clinical picture anywhere on a spectrum with pure nephritic and pure nephrotic syndromes at the extremes
PROTEINURIA
- hallmark of nephrotic syndromes
- 24 h urine protein: gold standard to assess degree of proteinuria
- urine ACR: used to screen for diabetic nephropathy
  - microalbuminuria
    - defined as ACR ≥2.8 mg/mmol (female) or ≥2.0 mg/mmol (male)
    - marker of vascular endothelial function
    - an important prognostic marker for kidney disease in DM and HTN (see Diabetes, NP28)
  - microalbuminuria is the earliest sign of diabetic nephropathy
- composition of normal total urine protein
  - upper limit of normal daily excretion of total protein is 150 mg/d
  - upper limit of normal daily excretion of albumin is 30 mg/d
  - the other normally excreted proteins are either filtered low molecular weight proteins (such as immunoglobulin light chains or β-2 microglobulin) or proteins secreted by the tubular epithelial cells (e.g. Tamm-Horsfall mucoprotein)

Table 8. Daily Excretion of Protein

<table>
<thead>
<tr>
<th>Daily Excretion</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 mg total protein (and &lt;30 mg albumin)</td>
<td>Normal</td>
</tr>
<tr>
<td>30-300 mg albumin</td>
<td>Microalbuminuria</td>
</tr>
<tr>
<td>&gt;3500 mg total protein/1.73m² BSA</td>
<td>Nephrotic range proteinuria</td>
</tr>
<tr>
<td>Variable amount of proteinuria</td>
<td>Can be seen with glomerular disease</td>
</tr>
<tr>
<td>Up to 2000 mg per d</td>
<td>Possible tubular disease because of failure to reabsorb filtered proteins</td>
</tr>
</tbody>
</table>
Investigations
- urine R&M, C&S, urea, Cr
- further workup (if degree of proteinuria >0.5 g/d, casts, and/or hematuria)
  - CBC, glucose, electrolytes, 24 h urine protein, and Cr
  - urine and serum immunoelectrophoresis, abdominal/pelvic U/S
  - serology: ANA, RF, p-ANCA (MPO), c-ANCA (PR3), Hep B, Hep C, HIV, ASOT
- indications for nephrology referral
  - generally, if there is “heavy” proteinuria (ACR >30 mg/mmol), should refer to nephrologist
  - definitely if there is nephrotic syndrome: marked proteinuria >3.5 g/1.73m²/d with hypoalbuminemia (<35 g/L)

HEMaturia
- hallmark of nephritic syndromes
- presence of blood or RBCs in urine
  - gross hematuria: pink, red, or tea-coloured urine
    - in gross hematuria, the urine should be centrifuged
      - if the sediment is red, true hematuria
      - if the supernatant is red, test for heme with a dipstick
        - if supernatant positive for heme: myoglobinuria or hemoglobinuria
        - if negative for heme: pseudohematuria; consider medications (e.g. rifampin), food dyes (e.g. beets), or metabolites (e.g. porphyria)
  - microscopic hematuria: blood in the urine that is invisible to the naked eye, >2-3 RBCs/HPF on microscopy

Figure 14. Approach to red urine

Investigations for Hematuria
- Hx and P/E: family history of nephrolithiasis, hearing loss (Alport’s), cerebral aneurysm (PCKD), diet, recent URTI, irritative and obstructive urinary symptoms (UTI)
- urine R&M, C&S, urea, Cr
- renal U/S
- 24 h urine stone workup if there is a history of stone formation or if there is a stone noted on imaging: calcium, oxalate, citrate, magnesium, uric acid, cysteine
- further workup (if casts and/or proteinuria): CBC, electrolytes, 24 h urine protein and Cr, serology (ANA, RF, C3, C4, p-ANCA, c-ANCA, ASOT)
- consider urology consult and possible cystoscopy if not clearly a nephrologic source for hematuria or if >50 yr of age

Glomerular Syndromes

1. ASYMPTOMATIC URINARY ABNORMALITIES

Clinical/Lab Features
- proteinuria (usually <2 g/d) and/or microscopic or macroscopic hematuria
  - isolated proteinuria
    - can be postural
    - occasionally can signal beginning of more serious GN (e.g. FSGS, IgA nephropathy, amyloid, diabetic nephropathy)
• hematuria with or without proteinuria
  • IgA nephropathy (Berger’s disease): most common type of primary glomerular disease
    worldwide, usually presents after viral URTI
  • hereditary nephritis (Alport’s disease): X-linked nephritis often associated with
    sensorineural hearing loss; proteinuria <2 g/d
  • thin basement membrane disease: usually autosomal dominant, without proteinuria;
    benign
  • benign recurrent hematuria: hematuria associated with febrile illness, exercise, or
    immunization; a diagnosis of exclusion after other possibilities are ruled out

2. NEPHRITIC SYNDROME

ACUTE NEPHRITIC SYNDROME
• a subset of nephritic syndrome in which the clinical course proceeds over days

Etiology
• etiology can be divided into low and normal complement levels
• frequently immune-mediated, with Ig and C3 deposits found in GBM
• outcome dependent on etiology

Clinical/Lab Features
• proteinuria (but <3.5 g/1.73 m²/d), abrupt onset hematuria (microscopic or macroscopic),
  azotemia (increased Cr and urea), RBC casts and/or dysmorphic RBCs in urine, oliguria, HTN
  (due to salt and water retention), peripheral edema/puffy eyes, smoky urine

RAPIDLY PROGRESSIVE GLOMERULONEPHRITIS/CRESCENTIC GLOMERULONEPHRITIS
• a subset of nephritic syndrome in which the clinical course proceeds over weeks to months
• clinical diagnosis, not histopathological
• any cause of GN can present as RPGN (except minimal change disease)
• additional etiologies seen only as RPGN: Goodpasture’s syndrome and granulomatosis with
  polyangitis (previously called Wegener’s granulomatosis)

Clinical/Lab Features
• fibrous crescents typically present on renal histopathology
• RBC casts and/or dysmorphic RBCs in urine
• classified by immunofluorescence staining
• Type I: Anti-GBM mediated (15% of cases)
• Type II: Immune Complex Mediated (24% of cases)
• Type III: Non-Immune Mediated (60% of cases)
• Type IV: Double Antibody Positive
• treatment: underlying cause for postinfectious; corticosteroids + cyclophosphamide or other
  cytotoxic agent + plasmaphoresis in select cases
• prognosis: 50% recovery with early treatment, depends on underlying cause

3. NEPHROTIC SYNDROME

Clinical/Lab Features
• heavy proteinuria (>3.5 g/1.73 m²/d)
• hypoalbuminemia
• edema
• hyperlipidemia (elevated LDL cholesterol), lipiduria (fatty casts and oval fat bodies on
  microscopy)
• hypercoagulable state (due to antithrombin III, Protein C, and Protein S urinary losses)
• patient may report frothy urine
• glomerular pathology on renal biopsy
  • minimal change disease (or minimal lesion disease or nil disease) – e.g. glomeruli appear
    normal on light microscopy
  • membranous glomerulopathy
  • focal segmental glomerulosclerosis (FSGS)
  • membranoproliferative GN
  • nodular glomerulosclerosis
• each can be idiopathic or secondary to a systemic disease or drug (sirolimus can cause
  proteinuria without obvious glomerular pathology)
### Table 9. Nephrotic Syndrome

<table>
<thead>
<tr>
<th>Secondary Causes</th>
<th>Membranous Glomerulopathy</th>
<th>Focal Segmental Glomerulosclerosis</th>
<th>Membranoproliferative Glomerulonephritis</th>
<th>Nodular Glomerulosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin's lymphoma</td>
<td>HBV, SLE, solid tumours</td>
<td>Reflux nephropathy, HK, HBV, obesity</td>
<td>HCV, malaria, SLE, leukemia, lymphoma, shunt nephritis</td>
<td>DM, amyloidosis</td>
</tr>
<tr>
<td>HBV, SLE, solid</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumours (lung, breast, GI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug Causes</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>Steroids</td>
</tr>
<tr>
<td>Gold, penicillamine</td>
<td>Steroids, ACEI/ARB for proteinuria</td>
</tr>
<tr>
<td>Heroin</td>
<td>Aspirin®, dipyridamole (Persantine®) – controversial</td>
</tr>
<tr>
<td></td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>

### 4. END STAGE RENAL DISEASE

- see *End Stage Renal Disease*, NP35

### INVESTIGATIONS FOR GLOMERULAR DISEASE

- **blood work**
  - first presentation: electrolytes, Cr, urea, albumin, fasting lipids
  - determining etiology: CBC, ESR, serum immunoelectrophoresis, anti-GBM, C3, C4, ANA, p-ANCA, c-ANCA, cryoglobulins, HBV and HCV serology, ASOT (anti-streptolysin titres), VDRL, HIV

- **urinalysis**: RBCs, WBCs, casts, protein
- **24 h urine for protein and CrCl**
- **radiology**
  - CXR (infiltrates, CHF, pleural effusion)
  - renal U/S
- **renal biopsy (percutaneous or open)** if heavy proteinuria or renal insufficiency and cause is not obviously diabetic nephropathy
- **urine immunoelectrophoresis**
  - for Bence-Jones protein if proteinuria present

### SECONDARY CAUSES OF GLOMERULAR DISEASE

**Amyloidosis**
- nodular deposits of amyloid in mesangium, usually related to amyloid light chain (AL)
- presents as nephrotic range proteinuria with progressive renal insufficiency
- can be primary or secondary
- secondary causes: multiple myeloma, TB, rheumatoid arthritis, malignancy

**Systemic Lupus Erythematosus**
- lupus nephritis can present as any of the glomerular syndromes
- nephrotic syndrome with an active sediment is most common presentation
- GN caused by immune complex deposition in capillary loops and mesangium with resulting renal injury
- serum complement levels are usually low during periods of active renal disease
- children and males with SLE are more likely to develop nephritis

**Figure 15. Approach to nephritic syndrome**

- Anti-GBM Mediated (RPGN Type I) (15%)
  - Linear IF pattern due to IgG and C3 deposition along capillary loops
  - anti-GBM +ve
  - With lung hemorrhage
    - Goodpasture’s disease
  - Without lung hemorrhage
    - Anti-GBM disease

- Immune Complex Mediated (RPGN Type II) (24%)
  - Granular pattern due to subendothelial or subepithelial deposits of IgG and C3
  - C3 normal
  - IgA nephropathy
    - Henoch-Schönlein purpura
  - Membranoproliferative GN
    - SLE
    - Infective endocarditis
    - Post-infectious GN
    - Cryoglobulinemia

- Non-Immune Mediated (RPGN Type III) (60%)
  - Pauci-immune: no immune staining
  - Decreased C3
  - Membranoproliferative GN
    - c-ANCA +ve
    - Granulomatosis with polyangiitis
  - p-ANCA +ve
    - Churg-Strauss
    - Microscopic polyangiitis

- Double Antibody Positive Disease (RPGN Type IV)
  - Has features of Type I and Type III
  - Double antibody positive
Figure 16. International Society of Nephrology/Renal Pathology Society classification of lupus nephritis 2003

Henoch-Schönlein Purpura
- seen more commonly in children
- purpura on buttocks and legs, abdominal pain, arthralgia, and fever
- glomeruli show varying degrees of mesangial hypercellularity
- IgA and C3 staining of mesangium
- usually benign, self-limiting course, 10% progress to CKD

Goodpasture’s Disease
- antibodies against type IV collagen present in lungs and GBM
- more common in 3rd and 6th decades of life, males slightly more affected than females
- present with RPGN type I and hemoptysis/dyspnea
- pulmonary hemorrhage more common in smokers and males
- treat with plasma exchange, cyclophosphamide, prednisone

ANCA-Associated Vasculitis (e.g. Granulomatosis with Polyangiitis and Microscopic Polyangiitis)
- PR3-ANCA (c-ANCA) most commonly associated with the clinical picture of granulomatosis with polyangiitis
- MPO-ANCA (p-ANCA) most commonly associated with the clinical picture of microscopic polyangiitis
- renal involvement very common
- focal segmental necrotizing RPGN with no immune staining
- may be indolent or fulminant in progression
- vasculitis and granulomas rarely seen on renal biopsy
- treatment typically involves cyclophosphamide and prednisone

Cryoglobulinemia
- cryoglobulins: monoclonal IgM and polyclonal IgG which precipitate at reduced temperatures
- presents as purpura, fever, Raynaud’s phenomenon, and arthralgias
- at least 50% of patients have hepatitis C
- renal disease seen in 40% of patients (isolated proteinuria/hematuria progressing to nephritic syndrome)
- most patients have decreased serum complement (C4 initially)
- treat hepatitis C, plasmapheresis
- overall prognosis: 75% renal recovery

Shunt Nephritis
- immune-complex mediated nephritis associated with chronically infected ventriculoatrial shunts inserted for treatment of hydrocephalus
- presents as acute nephritic syndrome with decreased serum complement
- nephrotic range proteinuria in 25% of patients

HIV-Associated Renal Disease
1. direct nephrotoxic effect of HIV infection, anti-retroviral drugs (e.g. tenofovir, indinavir), and other drugs used to treat HIV-associated infections
2. HIV-associated nephropathy
   - histology: focal and segmental glomerular collapse with mesangial sclerosis; “collapsing FSGS”
   - tubular cystic dilation and tubulo-recticular inclusions
   - clinical features: predominant in African American men, heavy proteinuria, progressive renal insufficiency
   - prognosis: kidney failure within 1 yr without treatment
   - therapy: short-term, high dose steroids, ACEI, HAART
**Infective Endocarditis**
- manifests as mild form of acute nephritic syndrome with decreased serum complement
- *S. aureus* is most common infecting agent
- treatment with appropriate antibiotics usually resolves GN

**Hepatitis B**
- can result in membranous nephropathy, polyarteritis nodosa, membranoproliferative GN

**Hepatitis C**
- can result in membranous nephropathy, cryoglobulinemia, and membranoproliferative GN

**Syphilis**
- can result in membranous GN

---

**Tubulointerstitial Disease**

### TUBULOINTERSTITIAL NEPHRITIS

**Definition**
- cellular infiltrates affecting primarily the renal interstitium and tubular cells
- functional tubule defects are disproportionately greater than the decrease in GFR
- classified as acute or chronic

**Signs and Symptoms**
- manifestation of disease depends on site of tubule affected
  1. proximal tubule (e.g. multiple myeloma, heavy metals)
     - Fanconi syndrome: decreased reabsorption in proximal tubule causing glycosuria, aminoaciduria, phosphaturia, hyperuricosuria
     - proximal RTA (decreased bicarbonate absorption): Type II RTA
  2. distal tubule (e.g. amyloidosis, obstruction)
     - distal RTA (Type I RTA), usually hypokalemic
     - Na⁺-wasting nephropathy
     - ± hyperkalemia leading to type IV RTA (where reduced renal bicarbonate production is caused by hyperkalemia)
  3. collecting duct (e.g. sickle cell anemia, analgesics, PCKD)
     - urinary concentrating defect leading to mild nephrogenic DI
     - polyuria

### 1. ACUTE TUBULOINTERSTITIAL NEPHRITIS

**Definition**
- rapid (days to weeks) decline in renal function
- 10-20% of all AKI

**Etiology**
- hypersensitivity
  1. antibiotics: β-lactams, sulfonamides, rifampin, quinolones, cephalosporins
  2. other: NSAIDs, allopurinol, furosemide, thiazides, triamterene, PPIs, acyclovir, phenytoin, cimetidine
- infections
- immune
  - SLE, acute allograft rejection, Sjögren's syndrome, sarcoidosis, mixed essential cryoglobulinemia
- idiopathic

**Pathophysiology**
- acute inflammatory cell infiltrates into renal interstitium

**Signs and Symptoms**
- AKI
- if hypersensitivity reaction: may see fever, skin rash, arthralgia, serum sickness-like syndrome (particularly rifampin)
- if pyelonephritis: flank pain and costovertebral angle (CVA) tenderness
- other signs and symptoms based on underlying etiology
- HTN and edema are uncommon
Investigations
- urine
  - mild, non-nephrotic range proteinuria and microscopic hematuria
  - sterile pyuria, WBC casts
  - eosinophils if AIN
- blood work
  - increased Cr and urea
  - eosinophilia if drug reaction
  - normal AG metabolic acidosis (RTA)
  - hypophosphatemia, hyperkalemia, hyponatremia
- gallium scan often shows intense signal due to inflammatory infiltrate
- renal biopsy definitive

Treatment
- treat underlying cause (e.g. stop offending medications, antibiotics if pyelonephritis)
- corticosteroids (may be indicated in allergic or immune disease)

Prognosis
- recovery within 2 wk if underlying insult can be eliminated
- the longer the patient is in renal failure, the less likely they will have a full renal recovery

2. CHRONIC TUBULOINTERSTITIAL NEPHRITIS

Definition
- characterized by slowly progressive renal failure, moderate proteinuria, and signs of abnormal tubule function

Etiology
- persistence or progression of acute TIN
- urinary tract obstruction: most important cause of chronic TIN (tumours, stones, bladder outlet obstruction, vesicoureteral reflux)
- chronic pyelonephritis due to vesicoureteral reflux or UTI with obstruction
- nephrotoxins
  - exogenous
    - analgesics: NSAIDs (common), acetaminophen
    - cisplatin, lithium, cyclosporine, tacrolimus
    - heavy metals (lead, cadmium, copper, lithium, mercury, arsenic)
    - Chinese herbs (aristolochic acid)
  - endogenous
    - hypercalcemia, hypokalemia, oxalate, uric acid
- vascular disease: ischemic nephrosclerosis, atheroembolic disease
- malignancies: multiple myeloma, lymphoma
- granulomatous: TB, sarcoidosis, granulomatosis with polyangiitis
- immune: SLE, Sjögren’s, cryoglobulinemia, Goodpasture's, amyloidosis, renal graft rejection, vasculitis
- hereditary: cystic diseases of the kidney, sickle cell disease
- others: radiation, Balkan (endemic) nephropathy

Pathophysiology
- fibrosis of interstitium with atrophy of tubules, mononuclear cell inflammation

Signs and Symptoms
- tubular dysfunction (e.g. acidosis, electrolyte disturbances)
- progressive renal failure with azotemia and uremia
- dependent on underlying etiology

Treatment
- stop offending agent or treat underlying disease
- supportive measures: correct metabolic disorders (Ca^{2+}, PO_{4}^{3-}) and anemia

Findings which Suggest Chronic Tubulointerstitial Nephritis
- normal AG metabolic acidosis
- hyperkalemia (out of proportion to degree of renal insufficiency)
- polyuria, nocturia
- partial or complete Fanconi’s syndrome
- urine: mild proteinuria, few RBCs and WBCs, no RBC casts
- U/S: shrunken kidneys with irregular contours
3. ACUTE TUBULAR NECROSIS

Definition
- abrupt and sustained decline in GFR within minutes to days after ischemic/nephrotoxic insult
- GFR reduced (this serves the purpose of avoiding life-threatening urinary loss of fluid and electrolytes from non-functioning tubules)

Etiology

![Figure 17. Etiology of ATN](image)

<table>
<thead>
<tr>
<th>Exogenous</th>
<th>Endogenous (bacterial)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>Endotoxins (bacterial)</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Myoglobin</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Hemoglobin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased Circulating Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemorrhage including post-surgical</td>
</tr>
<tr>
<td>Skin losses</td>
</tr>
<tr>
<td>GI losses</td>
</tr>
<tr>
<td>Renal losses</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Decreased Effective Circulating Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>Liver failure</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Anaphylaxis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vessel Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large or small renal artery involvement</td>
</tr>
</tbody>
</table>

Clinical Presentation
- typically presents as an abrupt rise in urea and Cr after a hypotensive episode, sepsis, rhabdomyolysis, or administration of nephrotoxic drug
- urine: high FE\textsubscript{Na}, pigmented-granular casts

Complications
- hyperkalemia: can occur rapidly and cause serious arrhythmias
- metabolic acidosis, decreased Ca\textsuperscript{2+}, increased PO\textsubscript{4}\textsuperscript{3-}, hypoalbuminemia

Investigations
- blood work: CBC, electrolytes, Cr, urea, Ca\textsuperscript{2+}, PO\textsubscript{4}\textsuperscript{3-}, blood gases
- urine: R&M, electrolytes, osmolality, microscopic urinalysis searching for pigmented granular casts
- ECG
- abdominal U/S
- rule out other causes of prerenal/postrenal azotemia and intrinsic AKI (GN, AIN, vasculitis)

Treatment
- largely supportive once underlying problem is corrected
- loop diuretics may help manage volume overload and reduce tubular metabolic requirements to allow for recovery (controversial)
- consider early dialysis in severe/rapidly progressing cases to prevent uremic syndrome

Prevention
- correct fluid balance before surgical procedures
- for patients with chronic renal disease requiring radiographic contrast:
  - give N-acetylcysteine 600-1200 mg PO bid day before and day of procedure, give intravenous isotonic fluid (either NaCl or NaHCO\textsubscript{3})
  - isotonic NaHCO\textsubscript{3} at 3 mL/kg over 1 h before procedure and 1 mL/kg/h for 6 h post-procedure if not contraindicated
  - avoid giving diuretics, ACEI, cyclosporine on morning of procedure if possible
- use renal-adjusted doses of nephrotoxic drugs in patients with renal insufficiency

Meta-Analysis: Effectiveness of Drugs for Preventing Contrast-Induced Nephropathy

Purpose: To determine the effectiveness of N-acetylcysteine, theophylline, fenoldopam, dopamine, kranosmin, furosemide, or mannitol on preventing nephropathy.

Study Selection: RCTs that used these agents in patients receiving iodinated contrast.

Results: In the 41 RCTs included N-acetylcysteine (RR=0.62 [0.44-0.88]) and theophylline (RR=0.49 [0.23-1.06]) reduced the risk of nephropathy more than saline alone. Furosemide increased the risk (RR=3.27 [1.40-7.26]). Other agents did not affect risk of nephropathy.

Conclusion: N-acetylcysteine is more renoprotective than hydration alone.
LARGE VESSEL DISEASE

Table 10. Summary of Vascular Diseases

<table>
<thead>
<tr>
<th>Large Vessel Disease</th>
<th>Small Vessel Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute renal artery occlusion (infarct)</td>
<td>Hypertensive nephrosclerosis</td>
</tr>
<tr>
<td>Renal artery stenosis (ischemia)</td>
<td>Atheroembolic renal disease</td>
</tr>
<tr>
<td>Renal vein thrombosis</td>
<td>Thrombotic microangiopathy</td>
</tr>
<tr>
<td></td>
<td>Scleroderma</td>
</tr>
<tr>
<td></td>
<td>Calcineurin inhibitor nephropathy</td>
</tr>
</tbody>
</table>

1. RENAL INFARCTION (ACUTE RENAL ARTERY OCCLUSION)
   - important, potentially reversible cause of renal failure

Etiology
   - abdominal trauma, surgery, embolism, extra-renal compression, hypercoagulable state, aortic dissection
   - kidney transplant recipients more vulnerable

Signs and Symptoms (depend on presence of collateral circulation)
   - fever, N/V, flank pain
   - leukocytosis, elevated AST, ALP
   - marked elevated LDH (LDH >4x upper limit of normal with minimal elevations in AST/ALT strongly suggestive)
   - acute onset HTN (activation of RAAS) or sudden worsening of long-standing HTN
   - renal dysfunction, e.g. elevated Cr (if bilateral, or solitary functioning kidney)

Investigations
   - renal arteriography (more reliable but risk of atheroembolic renal disease)
   - contrast-enhanced CT or MR angiography, duplex Doppler studies (operator dependent)

Treatment
   - prompt localization of occlusion and restoration of blood flow
   - anticoagulation, thrombolysis, percutaneous angioplasty or clot extraction, surgical thrombectomy
   - medical therapy in the long-term to reduce risk (e.g. antihypertensives)

2. ISCHEMIC RENAL DISEASE (RENAL ARTERY STENOSIS)
   - chronic renal impairment secondary to hemodynamically significant renal artery stenosis or microvascular disease
   - significant cause of ESRD: 15% in patients >50 yr (higher prevalence if significant vascular disease)
   - usually associated with large vessel disease elsewhere
   - causes of renal artery stenosis
     - atherosclerotic plaques (90%): proximal 1/3 renal artery, usually males >55 yr, smokers
     - fibromuscular dysplasia (10%): distal 2/3 renal artery or segmental branches, usually young females (typical onset <30 yr)
   - when there is decreased RBF, GFR is dependent on angiotensin II-induced efferent arteriolar constriction which raises the FF (GFR/RBF)
   - most common cause of secondary HTN (‘renovascular HTN’), 1-2% of all hypertensive patients
     - etiology
       - decreased renal perfusion of one or both kidneys leads to increased renin release and subsequent angiotensin production
       - increased angiotensin raises blood pressure in two ways
         1. causes generalized arteriolar constriction
         2. release of aldosterone increases Na⁺ and water retention
     - elevated blood pressure can in turn lead to further damage of kidneys and worsening HTN

Risk Factors
   - >50 yr
   - smoking
   - other atherosclerotic disease (dyslipidemia, DM, diffuse atherosclerosis)
Signs and Symptoms
- severe/refractory HTN and/or hypertensive crises, with negative family history of HTN
- asymmetric renal size
- epigastric or flank bruits
- spontaneous hypokalemia (renin activation in under-perfused kidney)
- increasing Cr with ACEI/ARB
- flash pulmonary edema with normal LV function

Investigations
- must establish presence of renal artery stenosis and prove it is responsible for renal dysfunction
- duplex Doppler U/S (kidney size, blood flow): good screening test (operator dependent)
- digital subtraction angiography (risk of contrast nephropathy)
- CT or MR angiography (effective noninvasive tests to establish presence of stenosis, for MR avoid gadolinium contrast if eGFR <30 mL/min because of risk of systemic dermal fibrosis)
- ACEI renography (e.g. captopril renal scan)
- renal arteriography (gold standard)

Treatment
- surgical: percutaneous angioplasty ± stent, surgical revascularization, occasionally surgical bypass
- medical: BP lowering medications (ACEI is drug of choice if unilateral renal artery disease but contraindicated if bilateral renal artery disease)
- little or no benefit if therapy is late (e.g. kidney is already shrunken), however, therapy can be considered to save the opposite kidney if normal

3. RENAL VEIN THROMBOSIS

Etiology
- hypercoagulable states (e.g. nephrotic syndrome, especially membranous), ECF volume depletion, extrinsic compression of renal vein, significant trauma, malignancy (e.g. RCC), sickle cell disease
- clinical presentation determined by rapidity of occlusion and formation of collateral circulation

Signs and Symptoms
- acute: N/V, flank pain, hematuria, elevated plasma LDH, ± rise in Cr, sudden rise in proteinuria
- chronic: PE (typical first presenting symptom), increasing proteinuria and/or tubule dysfunction

Investigations
- renal venography (gold standard), CT or MR angiography, duplex Doppler U/S

Treatment
- thrombolytic therapy ± percutaneous thrombectomy for acute renal vein thrombosis
- anticoagulation with heparin then warfarin (1 yr or indefinitely, depending on risk factors)

SMALL VESSEL DISEASE

1. HYPERTENSIVE NEPHROSCLEROSIS
- see Hypertension, NP31

2. ATHEROEMBOLIC RENAL DISEASE
- progressive renal insufficiency due to embolic obstruction of small- and medium-sized renal vessels by atheromatous emboli
- spontaneous or after renal artery manipulation (surgery, angiography, percutaneous angioplasty)
- anticoagulants and thrombolytics interfere with ulcerated plaque healing and can worsen disease
- investigations
  - eosinophilia, eosinophiluria, and hypocomplementemia
  - renal biopsy: needle-shaped cholesterol clefts (due to tissue-processing artifacts) with surrounding tissue reaction in small-/medium-sized vessels
- treatment
  - no effective treatment; avoid angiographic and surgical procedures in patients with diffuse atherosclerosis, medical therapy for concomitant cardiovascular disease
- prognosis: poor overall, at least one third will develop ESRD
3. THROMBOTIC MICROANGIOPATHY
- see Hematology, H30
- etiologies include the spectrum of TTP-HUS, DIC, severe preeclampsia
- renal involvement more common in HUS than TTP
- renal involvement characterized by fibrin thrombi in glomerular capillary loops ± arterioles
- treatment
  - depends on cause
  - supportive therapy
  - TTP-HUS: plasma exchange, corticosteroids (splenectomy and rituximab if refractory)
  - avoid platelet transfusions and ASA

4. CALCINEURIN INHIBITOR NEPHROPATHY
- cyclosporine and tacrolimus
- causes both acute reversible and chronic, largely irreversible nephrotoxicity
- major cause of kidney failure in other solid organ transplants (e.g. heart)
- acute: due to afferent and efferent glomerular capillary constriction leading to decreased GFR (tubular vacuolization)
  - prerenal azotemia
  - treatment: calcium channel blockers or prostaglandin analogs, reduce dose of cyclosporine or switch to another immunsuppressive drug
- chronic: result of obliterative arteriolopathy causing interstitial nephritis and CKD (striped fibrosis), less frequent now due to lower doses of calcineurin inhibitors

### Analgesic Nephropathies

1. Vasomotor AKI
- clinically: develop prerenal azotemia within a few days of starting NSAID
- normally prostaglandins vasodilate afferent renal arteriole to maintain blood flow
- NSAIDs act by blocking cyclooxygenase enzyme, thereby preventing prostaglandin synthesis and causing renal ischemia
- more common in elderly, underlying renal disease, hypovolemia (diuretics, CHF, cirrhosis, nephrotic syndrome)
- treatment: discontinue NSAID, dialysis rarely needed

2. Acute Interstitial Nephritis
- fenoprofen (60%), ibuprofen, naproxen
- may be associated with minimal change glomerulopathy and nephrotic range proteinuria
- resolves eventually with discontinuation of NSAID, may require interval dialysis
- short-term high dose steroids (1 mg/kg/d of prednisone) may hasten recovery

3. Chronic Interstitial Nephritis
- due to excessive consumption of antipyretics (phenacetin or acetaminophen) in combination with NSAIDs
- seen in patients who also have emotional stress, psychiatric symptoms, and GI disturbance
- papillary necrosis
  - gross hematuria, flank pain, declining renal function
  - calyceal filling defect seen with IVP – "ring sign"
- increased risk of transitional cell carcinoma of renal pelvis
- good prognosis if discontinue analgesics

4. Acute Tubular Necrosis
- can be caused by acetaminophen
  - incidence of renal dysfunction is related to the severity of acetaminophen ingestion
- vascular endothelial damage can also occur
- both direct toxicity and ischemia contribute to the tubular damage
- renal function spontaneously returns to baseline within 1-4 wk
- dialysis may be required during the acute episode of ingestion

5. Other Effects of NSAIDs
- sodium retention (2º to reduced GFR)
- hyperkalemia, HTN (2º to hyporeninemic hypoaldosteronism)
- excess water retention (2º to loss of antagonistic effect of prostaglandins on ADH)
Systemic Disease with Renal Manifestation

Diabetes

- diabetic nephropathy; presence of microalbuminuria or overt nephropathy (e.g. macroalbuminuria) in patients with DM who lack indicators of other renal diseases
- most common cause of end-stage renal failure in North America
- 35-50% of patients with type 1 DM will develop nephropathy, unknown percentage of type 2
- at diagnosis up to 30% of patients with type 2 DM have albuminuria (75% microalbuminuria, 25% overt nephropathy)
- microalbuminuria is a risk factor for progression to overt nephropathy and cardiovascular disease
- once macroalbuminuria is established, renal function declines, 50% of patients reach ESRD within 7-10 yr
- associated with HTN and diabetic retinopathy (especially type 1 DM) and/or neuropathy (especially type 2 DM)
- indication of possible non-diabetic cause of renal disease in patients with DM
  - rising Cr with little/no proteinuria
  - lack of retinopathy or neuropathy (microvascular complications)
  - persistent hematuria (microscopic or macroscopic)
  - signs or symptoms of systemic disease
  - inappropriate time course; rapidly rising Cr, renal disease in a patient with short duration of DM
  - family history of non-diabetic renal disease (e.g. PCKD, Alport’s)

DIABETIC RENAL COMPLICATIONS

1. Progressive Glomerulosclerosis
   - classic diabetic glomerular lesion; Kimmelstiel-Wilson nodular glomerulosclerosis (15-20%)
   - more common lesion is diffuse glomerulosclerosis with a uniform increase in mesangial matrix
   - Stage 1: Normal GFR
   - Stage 2: Detectable microalbuminuria (0-300 mg/24 h)
   - Stage 3: Macroalbuminuria (>300 mg/24 h)
   - Stage 4: Proteinuria (>500 mg/24 h)

2. Accelerated Atherosclerosis
   - common finding
   - may increase angiotensin II production resulting in increased BP
   - increased risk of ATN secondary to contrast media

3. Autonomic Neuropathy
   - affects bladder leading to functional obstruction and urinary retention
   - residual urine promotes infection
   - obstructive nephropathy

4. Papillary Necrosis
   - type 1 DM susceptible to ischemic necrosis of medullary papillae
   - sloughed papillae may obstruct ureter
   - can present as renal colic or with obstructive features ± hydroureteronephrosis

Table 11. Stages of Diabetic Progressive Glomerulosclerosis

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>† GFR (120-150%)</td>
<td>Detectable microalbuminuria</td>
<td>Macroalbuminuria (°300 mg/24 h)</td>
<td>† proteinuria (&gt;500 mg/24 h)</td>
</tr>
<tr>
<td>– compensatory hyperfiltration</td>
<td>(ACR 2.0-20 mg/mmol in men, 18-180 mg/d)</td>
<td>(ACR in men &gt;20 mg/mmol, (&gt;180 mg/d)</td>
<td>↓ GFR</td>
</tr>
<tr>
<td>± slightly increased mesangial matrix</td>
<td>ACR in women &gt;28 mg/mmol (&gt;250 mg/d)</td>
<td>Proteinuria (positive urine dipstick)</td>
<td>(&lt;20% glomerular filtration surface area present)</td>
</tr>
<tr>
<td></td>
<td>Normal GFR</td>
<td>Normal GFR</td>
<td>Sclerosed glomeruli</td>
</tr>
<tr>
<td></td>
<td>† † † mesangial matrix</td>
<td>† † † mesangial matrix</td>
<td></td>
</tr>
</tbody>
</table>

Figure 18. GFR and urine protein over time in DM

Protein Restriction for Diabetic Renal Disease
Cochrane DB Syst Rev 2007;4:CD002181

Purpose: To review the effects of dietary protein restriction on the progression of diabetic nephropathy.

Study Selection: RCTs and before and after studies of the effects of restricted protein diet on renal function in subjects with DM. 12 studies were reviewed.

Results: The risk of end-stage renal disease or death was lower in patients on low-protein diet. In patients with type 1 DM no effect on GFR was noted in the low-protein diet group.

Renoprotective Effect of Angiotensin-Receptor Antagonist Ibesartan in Patients with Nephropathy Due to Type 2 DM
NEJM 2001;345:851-860

Study: Multicentre, RCT, mean follow-up of 2.6 yr.

Patients: 808 patients (mean age 70 yr) with type 2 DM, HTN, and nephropathy (<24 h proteinuria >800 mg, serum Cr 09-265 umol/L, male), serum Cr 106-265 umol/L (female).

Intervention: BP control with Ibesartan vs. amiodipine vs. placebo, with use of adjuncts (not including ACEIs, ARBs, or CCB) as needed.

Outcomes: Primary composite endpoint included doubling of serum Cr, ESRD, or death. Secondary composite endpoint included morbidity and mortality from CVD causes.

Results: BP control was similar in all three arms. Ibesartan had a relative risk reduction of 25% vs. placebo and 23% vs. amiodipine for the primary end point. The Ibesartan group had a 3% risk reduction vs. placebo and 37% reduction vs. amiodipine for risk of doubling serum Cr. Serum Cr increased more slowly in the Ibesartan group versus placebo or amiodipine. No difference in absolute mortality or secondary end point.

Conclusion: Ibesartan conferred significant renoprotective benefits in patients with type 2 DM and nephropathy, independent of blood pressure lowering effects.
2013 Canadian Diabetes Association Clinical Practice Guidelines on Chronic Kidney Disease in Diabetes

- screen for microalbuminuria with a random urine test for albumin to Cr ratio (ACR) and eGFR with a serum Cr (e.g. using MDRD equation)
  - type 1 DM: annually in post-pubertal individuals after 5 yr of diagnosis
  - type 2 DM: at diagnosis, then annually
- If eGFR >60 mL/min or ACR <2.0 mg/mmol: there is no CKD, re-screen in 1 yr
- If urine ACR >20.0 mg/mmol: diagnose CKD
- If ACR <2.0 mg/mmol but >2.0 mg/mmol: order serum Cr for eGFR in 3 mo and 2 repeats of random urine ACRs over the next 3 mo; at 3 mo: if eGFR ≤60 mL/min or if >2/3 ACRs are >2.0 mg/mmol, diagnose CKD
- If CKD diagnosed, ordered urine R+M and dipstick, if negative then diagnose CKD in DM with CKD in DM: urine ACR and serum Cr (for eGFR) every 6 mo
- delay screening if transient cause of albuminuria or low eGFR
- evaluate for other causes of proteinuria, rule out non-diabetic renal disease
- avoid unnecessary potential nephrotoxins (NSAIDs, aminoglycosides, dye studies)

Priorities in the Management of Patients with DM

1. vascular protection for all patients with DM
   - ACEI, antiplatelet therapy (as indicated)
   - BP control, glycemic control, lifestyle modification, lipid control
2. optimization of BP in patients who are hypertensive
   - treat according to HTN guidelines
3. renal protection for DM patients with nephropathy (even in absence of HTN)
   - type 1 DM: ACEI
   - type 2 DM: CrCl >60 mL/min: ACEI or ARB; CrCl <60 mL/min: ARB
   - 2nd line agents: nondihydropyridine calcium channel blockers (diltiazem, verapamil)
   - combination of ACEI and ARB not recommended for proteinuria
   - check serum Cr and K+ levels within 1 wk of initiating ACEI or ARB and at time of acute illness
   - serum Cr can safely be allowed to rise up to 30% with initiation of ACEI or ARB, usually stabilizes after 2-4 wk, monitor for significant worsening of renal function or hyperkalemia
   - if >30% rise in serum Cr or hyperkalemia, discontinue medication and consider 2nd line agent
   - consider holding ACEI, ARB, and/or diuretic with acute illness and in women before becoming pregnant
   - consider referral to nephrologist if ACR >60 mg/mmol, eGFR <30 mL/min, progressive kidney function loss, unable to achieve BP targets, or unable to stay on ACEI or ARB

Scleroderma

- see Rheumatology, RH13
- 50% of scleroderma patients have renal involvement (mild proteinuria, high Cr, HTN)
- renal involvement usually occurs early in the course of illness
- histology: media thickened, “onion skin” hypertrophy of small renal arteries, fibrinoid necrosis of afferent arterioles and glomeruli
- 10-15% of scleroderma patients have a “scleroderma renal crisis” (occurs in first few years of disease): malignant HTN, ARF, microangiopathy, volume overload, visual changes, HTN encephalopathy
- treatment: BP control with ACEI slows progression of renal disease

Multiple Myeloma

- see Hematology, H49
- malignant proliferation of plasma cells in the bone marrow with the production of immunoglobulins
- patients may present with severe bone disease and renal failure
- light chains are filtered at the glomerulus and appear as Bence-Jones proteins in the urine (monoclonal light chains)
- kidney damage can occur by several mechanisms
  - hypercalcemia
  - light chain cast nephropathy or “myeloma kidney”
  - hyperuricemia
  - infection
  - secondary amyloidosis
  - monoclonal Ig deposition disease
  - diffuse tubular obstruction
  - light chain cast nephropathy
- large tubular casts in urine sediment (light chains + Tamm-Horsfall protein)
- proteinuria and renal insufficiency, can progress rapidly to kidney failure

References

-imen, J.; et al. The need for dialysis and early death among patients with renal crisis. Results: 61% of patients with renal crisis had good outcomes (95 had no dialysis and 24 received temporary dialysis), only 4 of these patients progressed to chronic renal failure and permanent dialysis. Greater than 50% of the patients who initially required dialysis discontinued it 5-18 mo later. Permanent dialysis or early death occurred in 39% of the patients.
-Conclusion: Renal crisis can be managed when HTN is aggressively controlled with ACEI.
• monoclonal Ig deposition disease
  - deposits of monoclonal Ig in kidney, liver, heart, and other organs
  - mostly light chains (85-90%)
  - causes nodular glomerulosclerosis (similar to diabetic nephropathy)
• lab features: increased BUN, increased Cr, urine protein immunoelectrophoresis positive for Bence-Jones protein (not detected on urine dipstick)
• poor candidates for kidney transplantation

**Malignancy**

• cancer can have many different renal manifestations
• kidney transplantation cannot be performed unless malignancy is cured
  - solid tumours: mild proteinuria or membranous GN
  - lymphoma: minimal change GN (Hodgkin’s) or membranous GN (non-Hodgkin’s)
  - renal cell carcinoma
  - tumour lysis syndrome: hyperuricemia, diffuse tubular obstruction
  - chemotherapy (especially cisplatin): ATN or chronic TIN
  - pelvic tumours/mets: postrenal failure secondary to obstruction
  - 2’ amyloidosis
  - radiotherapy (radiation nephritis)

**Chronic Kidney Disease**

**Definition**

• progressive and irreversible loss of kidney function
• abnormal markers (Cr, urea)
  - GFR <60 mL/min for >3 mo; or
  - kidney pathology seen on biopsy; or
  - decreased renal size on U/S (kidneys <9 cm)

**Clinical Features**

• volume overload and HTN
• electrolyte and acid-base balance disorders (e.g. metabolic acidosis)
• uremia

<table>
<thead>
<tr>
<th>Table 12. Stages of CKD (KDIGO, 2013)</th>
</tr>
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<tbody>
<tr>
<td><strong>Persistent Albuminuria Categories</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>G1</td>
</tr>
<tr>
<td>G2</td>
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<tr>
<td>G3a</td>
</tr>
<tr>
<td>G3b</td>
</tr>
<tr>
<td>G4</td>
</tr>
<tr>
<td>G5</td>
</tr>
</tbody>
</table>

The numbers in the boxes are a reflection of the risk of progression and are a guide to the frequency of monitoring/year

“D” is added to G5 for patients requiring dialysis

Classification is based on cause, GFR, and amount of albuminuria

Rate of progression and risk of complications are determined by the cause of CKD

**Management of Chronic Kidney Disease**

• diet
  - preventing HTN and volume overload
  - Na+ and water restriction
  - preventing electrolyte imbalances
  - K+ restriction (40 mmol/d)
  - PO43- restriction (1 g/d)
  - avoid extra–dietary Mg2+ (e.g. antacids)
  - preventing uremia and potentially delaying decline in GFR
  - protein restriction with adequate caloric intake in order to limit endogenous protein catabolism
• medical
  ▪ adjust dosages of renally excreted medications
  ▪ HTN: ACEI (target 130/80 or less), loop diuretics when GFR <25 mL/min
  ▪ dyslipidemia: statins
  ▪ calcium and phosphate disorders
    ▪ calcium supplements (e.g. TUMS®) treats hypocalcemia when given between meals and binds phosphate when given with meals
    ▪ consider calcitriol (1,25-dihydroxy-vitamin D) if hypocalcemic
    ▪ sevelamer (phosphate binder) if both hypercalcemic and hyperphosphatemic
    ▪ vitamin D analogues are being introduced in the near future
    ▪ cinacalcet for hyperparathyroidism (sensitizes parathyroid to Ca\textsuperscript{2+}, decreasing PTH)
  ▪ metabolic acidosis: sodium bicarbonate
  ▪ anemia: erythropoietin injections (hematocrit <30%); target hematocrit 33-36%
  ▪ clotting abnormalities: DDAVP if patient has clinical bleeding or invasive procedures (acts to reverse platelet dysfunction)
• dialysis (hemodialysis, peritoneal dialysis)
• renal transplantation

Prevention of Progression
• as above
• control of HTN, DM, cardiovascular risk factors (e.g. smoking cessation)
• avoid nephrotoxins
• address reversible causes of AKI

**Hypertension**

• see Family Medicine, FM35
• HTN occurs in about 20% of population
• etiology classified as primary ("essential"; makes up 90% of cases) or secondary
• primary HTN can cause kidney disease (hypertensive nephrosclerosis), which may in turn exacerbate the HTN
• secondary HTN can be caused by renal parenchymal or renal vascular disease

**Hypertensive Nephrosclerosis**

<table>
<thead>
<tr>
<th>Chronic Nephrosclerosis</th>
<th>Malignant Nephrosclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Histology</strong></td>
<td>Slow vascular sclerosis with ischemic changes affecting intralobular and afferent arterioles</td>
</tr>
<tr>
<td><strong>Clinical Picture</strong></td>
<td>Black race, underlying CKD, chronic hypertensive disease</td>
</tr>
<tr>
<td><strong>Urinalysis</strong></td>
<td>Mild proteinuria, normal urine sediment</td>
</tr>
<tr>
<td><strong>Therapy</strong></td>
<td>Blood pressure control, (target &lt;140/90) with frequent follow-up</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>Can progress to renal failure despite patient adherence</td>
</tr>
</tbody>
</table>

**Renovascular Hypertension**

• see Vascular Diseases of the Kidney, NP27

**Renal Parenchymal Hypertension**

• HTN secondary to GN, AIN, diabetic nephropathy, or any other chronic renal disease
• mechanism of HTN not fully understood but may include
  ▪ excess RAAS activation due to inflammation and fibrosis in multiple small intra-renal vessels
  ▪ production of unknown vasopressors, lack of production of unknown vasodilators, or lack of clearance of endogenous vasopressor
  ▪ ineffective sodium excretion with fluid overload

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Effects of Lowering LDL Cholesterol with Simvastatin and Ezetimibe in Patients with Chronic Kidney Disease

*Lancet* 2011;377:2181-2192

**Purpose:** To assess the efficacy and safety of the combination of simvastatin and ezetimibe in patients with moderate to severe CKD.

**Study:** Randomized, double-blind trial with 9,270 patients with CKD with no known history of myocardial infarction or coronary vascularization.

Patients were randomized to simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo.

**Primary Outcome:** First major atherosclerotic event (non-fatal myocardial infarction or coronary death, non-hemorrhagic stroke, or any arterial revascularization procedure).

**Results:** The simvastatin plus ezetimibe group was associated with an average LDL cholesterol difference of 0.85 mmol/L during a median follow-up of 4.9 yr. There was a 17% proportional reduction in major atherosclerotic events in the simvastatin plus ezetimibe group compared to placebo.

**Conclusions:** Reducing LDL cholesterol with a treatment regimen of simvastatin plus ezetimibe safely reduced the incidence of major atherosclerotic events in patients with moderate to severe CKD.
Investigations
- as well as investigations for renovascular HTN, additional tests may include
  - 24 h urinary estimations of CrCl and protein excretion
  - imaging (U/S, CT)
  - serology for collagen-vascular disease
  - renal biopsy

Treatment
- most chronic renal disease is irreversible, but treatment of HTN can slow the progression of renal insufficiency
- control ECF volume: Na+ restriction (2g/d intake), diuretic, dialysis with end-stage disease
- ACEI or ARB may provide added benefit (monitor K+ and Cr) if there is significant proteinuria (>300 mg/d)

Cystic Diseases of the Kidney
- characterized by epithelium-lined cavities filled with fluid or semisolid debris within the kidneys
- includes: simple cysts (present in 50% of population >50), medullary cystic kidney, medullary sponge kidney, polycystic kidney disease (autosomal dominant and recessive), and acquired cystic kidney disease (in chronic hemodialysis patients)

Adult Polycystic Kidney Disease
- autosomal dominant; at least 2 genes: \textit{PKD1} (chr 16p) and \textit{PKD2} (chr 4q)
- \textit{PKD1} (1:400), \textit{PKD2} (1:1,000) accounts for about 10% of cases of renal failure
- patients generally heterozygous for mutant polycystin gene but accumulate a series of second somatic hits precipitating the condition
- \textit{PKD1} encodes a protein that is responsible for cell-cell and cell-matrix interaction and sensing fluid flow by associating with cilia
- \textit{PKD2} encodes a protein that is a Ca\textsuperscript{2+} permeable nonselective cation channel that associates with cilia and is thought to control intracellular Ca\textsuperscript{2+} in response to flow
- defect leads to abnormal proliferation and apoptosis of tubular epithelial cells leading to cyst growth
- most common extrarenal manifestations: multiple asymptomatic hepatic cysts (33%), mitral valve prolapse (25%), cerebral aneurysm (10%), diverticulosis
- polycystic liver disease rarely causes liver failure
- less common extrarenal manifestations: cysts in pancreas, spleen, thyroid, ovary, seminal vesicles, and aorta

Signs and Symptoms
- often asymptomatic; discovered incidentally on imaging or by screening those with FHx
- acute abdominal flank pain/dull lumbar back pain
- hematuria (microscopic frequently initial sign, gross)
- nocturia (urinary concentrating defect)
- rarely extra-renal presentation (e.g. erupted berry aneurysm, diverticulitis)
- HTN (increased renin due to focal compression of intrarenal arteries by cysts) (60-75%)
- ± palpable kidneys

Common Complications
- urinary tract and cyst infections, HTN, chronic renal failure, nephrolithiasis (5-15%), flank and chronic back pain

Clinical Course
- polycystic changes are always bilateral and can present at any age
- clinical manifestations rare before age 20-25
- kidneys are normal at birth but may enlarge to 10x normal size
- variable progression to renal functional impairment (ESRD in up to 50% by age 60)

Investigations
- radiographic diagnosis: best accomplished by renal U/S (enlarged kidneys, multiple cysts throughout renal parenchyma, increased cortical thickness, splaying of renal calyces)
- CT abdo with contrast (for equivocal cases, occasionally reveals more cystic involvement)
- gene linkage analysis for \textit{PKD1} for asymptomatic carriers
- Cr, BUN, urine R&M (to assess for hematuria)
Treatment
- goal: to preserve renal function by prevention and treatment of complications
- educate patient and family about disease, its manifestations, and inheritance pattern
- genetic counselling: transmission rate 50% from affected parent
- prevention and early treatment of urinary tract and cyst infections (avoid instrumentation of GU tract)
- TMP/SMX, ciprofloxacin: able to penetrate cyst walls, achieve therapeutic levels
- adequate hydration to prevent stone formation
- avoid contact sports due to greater risk of injury to enlarged kidneys
- screen for cerebral aneurysms if family history of aneurysmal hemorrhages
- monitor blood pressure and treat HTN with ACEI
- dialysis or transplant for ESRD (disease does not recur in transplanted kidney)
- may require nephrectomy to create room for renal transplant

Medullary Sponge Kidney
- common, autosomal dominant, usually diagnosed in 4th-5th decades
- multiple cystic dilatations in the collecting ducts of the medulla
- renal stones, hematuria, and recurrent UTIs are common features
- an estimated 10% of patients who present with renal stones have medullary sponge kidney
- nephrocalcinosis on abdominal x-ray in 50% patients, often detect asymptomatic patients incidentally
- diagnosis: contrast filled medullary cysts on IVP leading to characteristic radial pattern (“bouquet of flowers”), “Swiss cheese” appearance on histological cross-section
- treat UTIs and stone formation as indicated
- does not result in renal failure

Autosomal Recessive Polycystic Kidney Disease
- 1:20,000 incidence
- prenatal diagnosis by enlarged kidneys
- perinatal death from respiratory failure
- patients who survive perinatal period develop CHF, HTN, CKD
- treated with kidney and/or liver transplant

End Stage Renal Disease
- ESRD represents a decline in kidney function requiring renal replacement therapy which can occur over days to weeks (AKI), over months to years (CKD), or as a combination of the two

Presentation of End Stage Renal Disease
1. Volume Overload
   - due to increase in total body Na⁺ content
   - signs: weight gain, HTN, pulmonary or peripheral edema
2. Electrolyte Abnormalities
   - high
     - K⁺ (decreased renal excretion, increased tissue breakdown)
     - PO₄³⁻ (decreased renal excretion, increased tissue breakdown)
     - Ca²⁺ (rare; happens during recovery phase after rhabdomyolysis-induced AKI or in settings where hypercalcemia contributes to renal failure, such as in multiple myeloma or sarcoidosis)
     - uric acid
   - low
     - Na⁺ (failure to excrete excessive water intake)
     - Ca²⁺ (decreased Vitamin D activation, hyperphosphatemia, hypoalbuminemia)
     - HCO₃⁻ (especially with sepsis or severe heart failure)
3. Uremic Syndrome
   - manifestations result from retention of urea and other metabolites as well as hormone deficiencies
Figure 19. Signs and symptoms of end stage renal disease

Complications
- CNS: decreased LOC, stupor, seizure
- CVS: cardiomyopathy, CHF, arrhythmia, pericarditis, atherosclerosis
- GI: peptic ulcer disease, gastroduodenitis, AVM
- hematologic: anemia, bleeding tendency (platelet dysfunction), infections
  - endocrine
    - decreased testosterone, estrogen, progesterone
    - increased FSH, LH
  - metabolic
    - renal osteodystrophy: secondary increased PTH due to decreased Ca^{2+}, high PO_{4}^{3-}, and low active vitamin D
    - osteitis fibrosa cystica
    - hypertriglyceridemia, accelerated atherogenesis
    - decreased insulin requirements, increased insulin resistance
- dermatologic: pruritus, ecchymosis, hemoptoma, calciphylaxis (vascular Ca^{2+} deposition)
Renal Replacement Therapy

Dialysis

Indications for Dialysis in Chronic Kidney Disease

Table 14. Indications for Dialysis

<table>
<thead>
<tr>
<th>Absolute Indications</th>
<th>Relative Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Volume overload*</td>
<td>• Anorexia</td>
</tr>
<tr>
<td>• Hyperkalemia*</td>
<td>• Decreased cognitive functioning</td>
</tr>
<tr>
<td>• Severe metabolic acidosis*</td>
<td>• Profound fatigue and weakness</td>
</tr>
<tr>
<td>• Neurologic signs or symptoms of uremia (encephalopathy, neuropathy, seizures)</td>
<td>• Severe anemia unresponsive to erythropoietin</td>
</tr>
<tr>
<td>• Uremic pericarditis</td>
<td>• Persistent severe pruritus</td>
</tr>
<tr>
<td>• Refractory accelerated HTN</td>
<td>• Restless leg syndrome</td>
</tr>
<tr>
<td>• Clinically significant bleeding diathesis</td>
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<tr>
<td>• Persistent severe N/V</td>
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<tr>
<td>• Plasma Cr &gt;1060 µmol/L or Urea &gt;36 mmol/L (clinical picture also important)</td>
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</tbody>
</table>

Table 15. Peritoneal Dialysis vs. Hemodialysis

<table>
<thead>
<tr>
<th>Rate</th>
<th>Peritoneal Dialysis</th>
<th>Hemodialysis</th>
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</thead>
<tbody>
<tr>
<td>Slow</td>
<td></td>
<td>Fast</td>
</tr>
<tr>
<td>Location</td>
<td>Home</td>
<td>Hospital (usually)</td>
</tr>
<tr>
<td>Ultrafiltration</td>
<td>Osmotic pressure via dextrose dialysate</td>
<td>Hydrostatic pressure</td>
</tr>
<tr>
<td>Solute Removal</td>
<td>Concentration gradient and convection</td>
<td>Concentration gradient and convection</td>
</tr>
<tr>
<td>Membrane</td>
<td>Peritoneum</td>
<td>Semi-permeable artificial membrane</td>
</tr>
<tr>
<td>Method</td>
<td>Indwelling catheter in peritoneal cavity</td>
<td>Line from vessel to artificial kidney</td>
</tr>
<tr>
<td>Complications</td>
<td>Infection at catheter site</td>
<td>Vascular access (clots, collapse)</td>
</tr>
<tr>
<td></td>
<td>Bacterial peritonitis</td>
<td>Bacteremia</td>
</tr>
<tr>
<td></td>
<td>Metabolic effects of glucose</td>
<td>Bleeding due to heparin</td>
</tr>
<tr>
<td></td>
<td>Difficult to achieve adequate clearance in patients with large body mass</td>
<td>Hemodynamic stress of extracorporeal circuit</td>
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<tr>
<td></td>
<td></td>
<td>Disequilibrium syndrome (headache, cerebral edema, hypotension, nausea, muscle cramps related to solute/water flux over short time)</td>
</tr>
<tr>
<td>Preferred When</td>
<td>Young, high functioning, residual renal function</td>
<td>Bed-bound, comorbidities, no renal function</td>
</tr>
<tr>
<td>Success depends on presence of residual renal function</td>
<td>Residual renal function not as important</td>
<td></td>
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</tbody>
</table>

*Unresponsive to medications

• hemodialysis: blood is filtered across a semipermeable membrane removing accumulated toxic waste products, solutes, excess fluid (ultrafiltration), and restoring buffering agents to the bloodstream
  • available as intermittent (e.g. 3x/wk), continuous (CVVHD) or sustained low efficiency (SLED)
  • can be delivered at home or in-centre, nocturnal
  • vascular access can be achieved through a central line, an artificial graft, or an AV fistula
• patients with CKD should be referred for surgery to attempt construction of a primary AV fistula when their eGFR is <20 mL/min, the serum Cr level quoted as >350 µmol/L, or within 1 yr of an anticipated need
• peritoneal dialysis: peritoneum acts as a semipermeable membrane similar to hemodialysis filter
  • advantages: independence, fewer stringent dietary restrictions, better rehabilitation rates
  • available as continuous ambulatory (CAPD; four exchanges per day) or cyclic (CCPD; machine carries out exchanges overnight)
• refer patients with chronic renal disease to a nephrologist early on to facilitate treatment and plan in advance for renal replacement therapy (RRT)

When to Initiate Dialysis

CrCl <20 mL/min
• Educate patient regarding dialysis; if not a candidate for peritoneal dialysis, make arrangements for AV fistula
CrCl <15 mL/min
• Weigh risk and benefits for initiating dialysis
CrCl <10 mL/min
• Dialysis should be initiated

NOTE
• Cockcroft-Gault equation (or MDRD equation) should be used to measure kidney function
• Monitor for uremic complications
• Significant benefits in quality of life can occur if dialysis started before CrCl <15 mL/min
• It is unclear whether patients who start dialysis early have increased survival
• A preemptive transplant can be considered if patient is stable, in order to avoid dialysis

Commonly Used Immunosuppressive Drugs

Calcineurin inhibitors
• Cyclosporine
• Tacrolimus

Antiproliferative medications
• Mycophenolate mofetil
• Azathioprine

Other agents
• Sirolimus
• Prednisone

Anti-lymphocyte antibodies
• Thymoglobin
• Basiliximab
**Renal Transplantation**

- provides maximum replacement of GFR
- preferred modality of RRT in CKD, not AKI
  - best way to reverse uremic signs and symptoms
  - only therapy shown to improve survival in CKD patients with ESRD
- native kidneys usually left in situ
- 2 types: deceased donor, living donor (related or unrelated)
- kidney transplanted into iliac fossa, transplant renal artery anastomosed to external iliac artery of recipient
- 1 yr renal allograft survival rates ≥90%

**Complications**
- acute rejection: graft site tenderness, rise in Cr, oliguria, ± fever, although symptoms are uncommon
- leading causes of late allograft loss: interstitial fibrosis/tubular atrophy (IFTA) and death with functioning graft
- #1 cause of mortality in transplanted patients is cardiovascular disease
- immunosuppressant drug therapy: side effects include infections, malignancy (skin, Kaposi's sarcoma, post-transplant lymphoproliferative disorder)
- *de novo* GN (usually membranous)
- new-onset DM (often due to prednisone use)
- cyclosporine or tacrolimus nephropathy (see *Small Vessel Disease*, NP18)
- chronic allograft nephopathy
  - early allograft damage caused by episodes of acute rejection and acute peritransplant injuries
  - immunologic and nonimmunologic factors (HTN, hyperlipidemia, age of donor, quality of graft, new onset DM)
  - transplant glomerulopathy from antibody injury causes nephrotic proteinuria
- CMV (cytomegalovirus) infection and other opportunistic infections usually occur between 1 and 6 mo post-transplant
- BK virus (polyoma virus) nephropathy can result from over-immunosuppression and lead to graft loss
# Table 16. Common Medications in Nephrology

<table>
<thead>
<tr>
<th>Classification</th>
<th>Examples</th>
<th>Site of Action</th>
<th>Mechanism of Action (Secondary Effect)</th>
<th>Indication</th>
<th>Dosing</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loop Diuretics</strong></td>
<td>furosemide (Lasix®)</td>
<td>Thick ascending limb of Loop of Henle</td>
<td>↓ Na⁺ /↓K⁺/↑O₂ remodel renal and peripheral vasodilatory effects (K⁺ loss; ↑ H⁺ secretion; ↑ Ca²⁺ excretion)</td>
<td>Management of edema secondary to CHF; nephrotic syndrome, cirrhotic ascites; ↑ free water clearance (e.g., in SIADH-induced hypotension); ↓ BP (less effective due to short action)</td>
<td>furosemide: edema: 20-80 mg IV/IM/PO q6-8h (max 600 mg/d) until desired response. HTN: 20-80 mg/d PO OD/bid dosing</td>
<td>Allergy in sulfon-sensitivities. Electrolyte abnormalities: hypokalemia, hyponatremia. Hypercalciuria, hypercalciuria (with stone formation). Volume depletion with metabolic alkalosis. Precipitates gout attacks.</td>
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<tr>
<td></td>
<td>bumetanide (Bumex®)</td>
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<td></td>
<td>ethacrynic acid (Edecrin®)</td>
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<td>torsemide (Demadex®)</td>
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<td></td>
<td>chlorothiazide (Diuril®)</td>
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<td></td>
<td>hydrochlorothiazide (HCTZ)</td>
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<td>indapamide (Lozole®/Lozide®)</td>
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<td>metolazone (Zaroxolyn®)</td>
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<td>triamterene (Dyrenium®)</td>
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<td></td>
<td>amiloride (Midamor®)</td>
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<tr>
<td><strong>Combination Agents</strong></td>
<td>Dyazide® (Triamterene + HCTZ)</td>
<td></td>
<td>Combination of ACEI and thiazide</td>
<td>Have a synergistic effect.</td>
<td>Add to thiazide to reduce hypokalemia.</td>
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<tr>
<td></td>
<td>Aldactazide® (spironolactone + HCTZ)</td>
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<td></td>
<td>Moduretic® (amiloride + HCTZ)</td>
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<td></td>
<td>Vasenetic® (enalapril + HCTZ)</td>
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<td></td>
<td>Zestoretic® (lisinopril + HCTZ)</td>
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<tr>
<td><strong>Osmotic Diuretics</strong></td>
<td>mannitol (Osmitrol®)</td>
<td>Renal tubules (proximal and collecting duct)</td>
<td>Non-reabsorbable solutes increase osmotic pressure of glomerular filtrate; inhibits reabsorption of water and ↑ urinary excretion of toxic materials</td>
<td>To ↓ intracranial or intracranial pressure. Mobilization of excess fluid in renal failure or edematous states.</td>
<td>Mannitol: JVP: 0.25-2 g/kg IV over 30-60 min</td>
<td>Transient volume expansion. Electrolyte abnormalities: ↓↓ Na⁺, ↓↓ K⁺.</td>
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<td></td>
<td>glycerol</td>
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<tr>
<td></td>
<td>enalapril (Vasotec®)</td>
<td></td>
<td>Prevents angiotensin II vasococontracting vascular smooth muscle → net vasoconstriction → ↓ BP</td>
<td>Cardioselective use; 10 mg PO OD.</td>
<td>Trandolapril: HTN: 1-4 mg PO OD.</td>
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<tr>
<td></td>
<td>lisinopril (Prinivil®)</td>
<td></td>
<td>Prevents angiotensin II mediated aldosterone release from adrenal cortex and action on proximal renal tubules → ↑ Na⁺ and H₂O excretion → ↓ BP</td>
<td>Renoprotective effects.</td>
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<td></td>
<td>trandolapril (Mavik®)</td>
<td></td>
<td>Reduces fibrosis and arteriosclerosis</td>
<td>Cardioprotective effects (see Cardiology and Cardiac Surgery, C31, C38).</td>
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<tr>
<td></td>
<td>captopril (Capoten®)</td>
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<tr>
<td><strong>ARB</strong></td>
<td>losartan (Cozaar®)</td>
<td>Vascular smooth muscle, arterial cortex, proximal tubules</td>
<td>Competitive inhibitor at the angiotensin II receptor; prevents angiotensin II vasococontracting action on vascular smooth muscle → ↓ BP</td>
<td>Cardioprotective effects (see Cardiology and Cardiac Surgery, C31, C38).</td>
<td>Losartan 25-100 mg PO OD. Candesartan 8-22 mg PO OD.</td>
<td>Hyperkalemia. Caution – reduce dose in hepatic impairment. AKI. Teratogenic.</td>
</tr>
<tr>
<td></td>
<td>candesartan (Atacand®)</td>
<td></td>
<td>Prevents angiotensin II mediated aldosterone release from arterial cortex and action on proximal renal tubules → ↑ Na⁺ and H₂O excretion</td>
<td>Renoprotective effects.</td>
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<td>valsartan (Diovan®)</td>
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<td>telmisartan (Micardis®)</td>
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<td>eprosartan (Teveten®)</td>
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<td></td>
<td>olmesartan (Olmetec®)</td>
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<tr>
<td><strong>Renin Antagonists</strong></td>
<td>aliskiren (Rasilez®)</td>
<td>Direct renin antagonist</td>
<td>Inhibits renin production and activity</td>
<td>Cardioprotective and renoprotective abilities being evaluated.</td>
<td>Aliskiren 150-300 mg PO OD.</td>
<td>Hyperkalemia.</td>
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</table>
## Landmark Nephrology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>4D</td>
<td>NEJM 2005; 353:238-48</td>
<td>Patients with type 2 DM receiving maintenance hemodialysis were randomized to 20 mg of atorvastatin per day or matching placebo; no difference in composite index of death from cardiac causes, nonfatal myocardial infarction, and stroke</td>
</tr>
<tr>
<td>AASK</td>
<td>JAMA 2001; 285:2719-28</td>
<td>Ramipril, compared with amldopine, slows progression of hypertensive renal disease and proteinuria and may benefit patients without proteinuria as well</td>
</tr>
<tr>
<td>ACCOMPLISH</td>
<td>NEJM 2008; 359:2417-28</td>
<td>Combination treatment with an ACEI and a CCB (benazepril-amldopine) was more successful than a combination of ACEI and a thiazide diuretic (benzapril-HCTZ) in reducing cardiovascular events in patients with HTN who were at risk for such events</td>
</tr>
<tr>
<td>ACEI and Diabetic</td>
<td>NEJM 1993; 329:1456-62</td>
<td>Captopril protects against deterioration in renal function in insulin-dependent diabetic nephropathy and is significantly more effective than blood pressure control alone</td>
</tr>
<tr>
<td>ALERT</td>
<td>Lancet 2003; 361:2024-31</td>
<td>The use of fluvastatin in renal transplant recipients did not significantly decrease the risk of the occurrence of a major adverse cardiac event (defined as cardiac death, non-fatal MI, or coronary intervention procedure) compared with placebo; however, there was a significant reduction in cardiac deaths or non-fatal MI</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>Early Termination (Unpublished Results; protocol – ADT 2009; 24:1663-171)</td>
<td>Combining Aliskiren with ACEI or ARB in high-risk patients with type 2 DM leads to increased incidence of nonfatal stroke, hyperkalemia, and hypertension</td>
</tr>
<tr>
<td>ASTRAL</td>
<td>NEJM 2009; 361:1953-62</td>
<td>Renal artery revascularization compared to medical therapy does not improve renal function, BP, renal or cardiovascular events, or mortality, and carries significant operative risks</td>
</tr>
<tr>
<td>AURORA</td>
<td>NEJM 2009; 360:1395-407</td>
<td>Patients receiving maintenance hemodialysis randomized to rosuvastatin 10 mg daily or placebo; rosuvastatin lowered the LDL cholesterol level but had no significant effect on the composite primary end point of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke</td>
</tr>
<tr>
<td>BENEDICT</td>
<td>NEJM 2004; 351:1941-51</td>
<td>Treatment with ACEI trandolapril alone or trandolapril combined with verapamil decreased the incidence of microalbuminuria in patients with type 2 DM and HTN with normoalbuminuria</td>
</tr>
<tr>
<td>CHOIR</td>
<td>NEJM 2006; 355:2085-98</td>
<td>Patients with CKD were randomly assigned to receive a dose of epoetin alfa targeted to achieve a hemoglobin level of 135 g/L or 113 g/L; the higher target group had an increased risk of death, myocardial infarction, hospitalization for congestive heart failure (without renal replacement therapy), or stroke</td>
</tr>
<tr>
<td>CORAL</td>
<td>NEJM 2014; 370:13-22</td>
<td>Renal-artery stenting did not confer a significant benefit with respect to the prevention of renal or cardiac events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease</td>
</tr>
<tr>
<td>CREATE</td>
<td>NEJM 2006; 355:2071-84</td>
<td>Patients with CKD (15-35 mL/min) and mild to moderate anemia (110-125 g/L) were randomized to normal (130-150 g/L) or sub-normal (105-115 g/L) hemoglobin levels; early and complete correction of hemoglobin did not reduce the risk of cardiovascular events</td>
</tr>
<tr>
<td>DETAIL</td>
<td>NEJM 2004; 351:1952-61</td>
<td>The ARB telmisartan and the ACEI enalapril are equally effective in slowing renal function deterioration in type 2 DM with mild to moderate HTN and early nephropathy</td>
</tr>
<tr>
<td>ELITE-SYMPHONY</td>
<td>NEJM 2007; 357:2562-75</td>
<td>Daclizumab induction, MMF, steroids, and low-dose tacrolimus effectively maintain stable renal function following renal transplantation, without the negative effects on renal function commonly reported for standard CNI regimens</td>
</tr>
<tr>
<td>FHN</td>
<td>NEJM 2010;363:2287-300</td>
<td>Patients were randomized to dialysis 6x/wk (frequent) or 3x/wk (conventional); frequent hemodialysis was associated with improvement in composite outcomes of death, or change in left ventricular mass and death, or change in a physical-health composite score; frequent hemodialysis caused more frequent interventions related to vascular access</td>
</tr>
<tr>
<td>HEMO</td>
<td>NEJM 2002; 344:1907-17</td>
<td>Use of high dose dialysis or high flux membranes versus standard dose or low flux in thrice-weekly dialysis does not improve survival or outcomes; possible benefit in cardiac-related outcomes with high flux membranes</td>
</tr>
<tr>
<td>IDEAL</td>
<td>NEJM 2010; 363:609-19</td>
<td>Patients with progressive CKD and GFR between 10 and 15 mL/min randomized to initiate dialysis at GFR of 10-14 mL/min (early) or 5-7 mL/min (late); early initiation of dialysis in patients with stage G5 CKD was not associated with an improvement in survival or clinical outcomes</td>
</tr>
<tr>
<td>IDNT</td>
<td>NEJM 2001; 345:851-60</td>
<td>Treatment with ibrsartan reduced the risk of developing end-stage renal disease and worsening renal function in patients with type 2 DM and diabetic nephropathy</td>
</tr>
<tr>
<td>IRMA</td>
<td>NEJM 2001; 345:870-8</td>
<td>Ibrsartan is renoprotective independently of its blood pressure lowering effect in patients with type 2 DM and microalbuminuria</td>
</tr>
<tr>
<td>MDRD</td>
<td>Ann Intern Med 1995; 123:754-62</td>
<td>Patients with proteinuria of more than 1 g/d should have a target BP &lt;125/75 mmHg; patients with proteinuria of 0.25 to 1.0 g/d should have a target BP &lt;130/80 mmHg</td>
</tr>
<tr>
<td>ONTARGET</td>
<td>Lancet 2008; 372:547-53</td>
<td>Telmisartan and ramipril monotherapy reduced proteinuria and rise in Cr in patients with high vascular risk; combination of the two agents led to increased acute renal failure episodes, syncope, and hypotension</td>
</tr>
<tr>
<td>REIN</td>
<td>Lancet 1999; 354:359-64</td>
<td>In non-diabetic nephropathy, ACEI were renoprotective in patients with non-nephrotic range proteinuria</td>
</tr>
<tr>
<td>REIN2</td>
<td>Lancet 2005; 365:939-46</td>
<td>In non-diabetic nephropathy already on ACEI, no further benefit from intensified BP control (sBP/dBP&lt;130/80 mmHg) by adding a CCB versus conventional BP control (dBP&lt; 90 mmHg) on ACEI alone</td>
</tr>
<tr>
<td>RENAAAL</td>
<td>NEJM 2001; 345:861-9</td>
<td>Losartan conferred significant renal benefits in patients with type 2 DM and nephropathy and was generally well-tolerated</td>
</tr>
<tr>
<td>RENAL</td>
<td>NEJM 2009; 361:1627-38</td>
<td>High intensity continuous renal-replacement therapy in AKI does not improve survival or outcomes compared to low intensity treatment, and is associated with higher rates of hypophosphatemia</td>
</tr>
<tr>
<td>Trial</td>
<td>Reference</td>
<td>Results</td>
</tr>
<tr>
<td>-----------------------</td>
<td>-----------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Rituximab in ADPKD</td>
<td>NEJM 2012; 367:2407-18</td>
<td>Tolupratin (vs. placebo) slowed the increase in total kidney volume and decline in kidney function over a 3-year period in patients with ADPKD but was associated with a higher discontinuation rate, due to adverse events</td>
</tr>
<tr>
<td>ROAD</td>
<td>JASN 2007; 18:1889-98</td>
<td>Uptitration of either ACEI benazepril or ARB losartan to optimal anti-proteinuria doses conferred benefit on renal outcome in patients without DM who had proteinuria and renal insufficiency</td>
</tr>
<tr>
<td>ROADMAP</td>
<td>NEJM 2011; 364:907-17</td>
<td>The use of the ARB olmesartan was more effective than placebo in delaying the onset of microalbuminuria in patients with type 2 DM, normoalbuminuria, and good blood pressure control; however, a higher rate of fatal cardiovascular events was found amongst patients with preexisting coronary heart disease in the olmesartan group</td>
</tr>
<tr>
<td>SHARP</td>
<td>Lancet 2011; 377:2181-92</td>
<td>Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization took simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo; simvastatin 20 mg plus ezetimibe 10 mg daily resulted in reduction of LDL cholesterol with associated reduction of major atherosclerotic events in patients with CKD</td>
</tr>
<tr>
<td>TREAT</td>
<td>NEJM 2009; 361:2019-32</td>
<td>Patients with type 2 DM, CKD, and anemia were randomized to darbepoetin targeting a hemoglobin of 13 g/dL or placebo; darbepoetin did not reduce the risk of death, a cardiovascular event, or a renal event, and was associated with an increased risk of stroke</td>
</tr>
</tbody>
</table>

### References


Lancet 2011;377:2181-92 Randomized placebo-controlled trial in patients with CKD and no history of MI or coronary revascularization took simvastatin 20 mg plus ezetimibe 10 mg daily versus matching placebo; simvastatin 20 mg plus ezetimibe 10 mg daily resulted in reduction of LDL cholesterol with associated reduction of major atherosclerotic events in patients with CKD

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Lee MS, McCullough AJ, Feinendegen LE, et al. Hemodialysis in patients with ADPKD but was associated with a higher discontinuation rate, due to adverse events


Ontarget Investigators. Telmisartan, ramipril, or both in patients at high risk for vascular events. NEJM 2008;358:1547-1559.


Neurology

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Acronyms

ACA anterior cerebral artery
ACh acetylcholine
AD Alzheimer’s disease
ADL activities of daily living
AED antiepileptic drugs
AION acute ischemic optic neuropathy
ALS amyotrophic lateral sclerosis
AVM arteriovenous malformation
AVPU alert, verbal, pain, unresponsive
CJD Creutzfeldt-Jakob disease
CN cranial nerve
CNS central nervous system
CRVO central retinal vein occlusion
CSF cerebral spinal fluid
CVD cerebrovascular disease
DBS deep brain stimulation
DLB dementia with Lewy bodies
DM diabetes mellitus
EOM extraocular movement
EDH ethanol
EEG extracranial movement
ETF frontal eye field
FTD frontotemporal dementia
GBS Guillain-Barré syndrome
GCA giant cell arteritis
GCS Glasgow coma scale
GPH Globus pallidus pars externa
GR Globus pallidus pars interna
HD Huntington’s disease
IADL instrumental activities of daily living
ICL intracranial hemorrhage
ICP intracranial pressure
ICH intracranial hypertension
IIH idiopathic intracranial hypertension
INOP interneuronal ophthalmoplegia
IVIG intravenous immunoglobulin
JC John Cunningham virus
LEMS Lambert-Eaton myasthenic syndrome
LGB lateral geniculate body
LMN lower motor neuron
LOC level of consciousness
LP lumbar puncture
MCA middle cerebral artery
MGG myasthenia gravis
MFL medial longitudinal fasciculus
MMSE mini mental status examination
MoCA Montreal cognitive assessment
MS multiple sclerosis
NCS nerve conduction studies
NAG neurogenic ataxia
NPA normal pressure hydrocephalus
PCCom posterior communicating artery
PD Parkinson’s disease
PIAG posterior inferior cerebellar artery
PLMS periodic limb movement in sleep
PPA primary progressive aphasia
PPN paramedian pontine reticular formation
PSG progressive supranuclear palsy
RAPD relative afferent pupillary defect
REM rapid eye movement
RLS restless legs syndrome
ROM range of motion
SAH subarachnoid hemorrage
SEH subdural hematoma
SNHL substantia nigra pars compacta
SNHL substantia nigra pars reticulata
STN subthalamus nucleus
TBI traumatic brain injury
TIA transient ischemic attack
UMN upper motor neuron
VEGF vascular endothelial growth factor
VZV varicella zoster virus

Approach to the Neurological Complaint

• Two questions: Where is the lesion? What is the lesion?

Lesion Localization

• cortical
  • contralateral paresis (with differential effect on face and arm vs leg)
  • UMN injury (normal tone, hyperreflexia, Babinski sign, spasticity, no atrophy)
  • homonymous hemianopia midline
  • cortical sensory loss (hemisensory loss, position sense, two-point discrimination, graphesthesia, stereognosis)
  • dominant hemisphere (aphasia, alexia, agraphia, acalculia, left-right disorientation)
  • non-dominant hemisphere syndromes (hemineglect, dysprosody, amusia, constructional apraxia)
  • homonymous hemianopia/quadrantanopia
  • gaze deviation (eyes look toward infarct side of the lesion)
  • partial seizure
  • agnosia (visual, auditory)
  • apraxia
  • dominant hemisphere (aphasia, syndromes (alexia, without agraphia, acalculia, Gerstmann syndrome)
  • non-dominant hemisphere syndromes (denial, hemineglect, constructional apraxia)
  • alien hand syndrome

• subcortical white matter:
  • internal capsule: contralateral paresis with equal face, arm, leg involvement without sensory/cortical deficits; contralateral dysmetria/clumsiness and leg paresis
  • basal ganglia: pill-rolling tremor, bradykinesia, festinating gait, hemiballismus, chorea, dystonic posture (basal ganglia)
  • thalamus: dense sensory loss (thalamic), contralateral severe pain

• brainstem: (bulbar)
  • cranial nerve deficits
  • crossed hemiplegia or sensory loss (i.e. ipsilateral face, contralateral body)
  • crossed sensory loss
  • dysmetria
  • ipsilateral cerebellar (rapid alternating movements, tandem gait)
  • nystagmus toward lesion, diplopia, INO (impaired adduction on contralateral gaze)
  • dysphagia
  • dysarthria (impaired speech articulation)
  • hearing loss
  • vertigo

• cerebellum
  • ipsilateral ataxia (unsteadiness, incoordination)
  • dysmetria
  • intention tremor
  • dysdiadochokinesia
  • wide-based gait, truncal titubation (staggers, reeling, lurching)
  • scanning speech (explosive speech with noticeable pauses and accentuated syllables)
  • nystagmus, distorted smooth pursuit, oscillopsia
• spinal cord
  ▪ absence of facial involvement with bilateral motor and/or sensory deficits below the lesion without facial involvement
  ▪ sphincter dysfunction
  ▪ ataxia, sensory level (sharp line below which there is decreased sensation); sensory deficits exist; suspended "cape-like" sensory level
  ▪ LMN signs (flaccid paresis, hypotonia, hyporeflexia, atrophy, fasciculations) at level of lesion; UMN signs below lesion (marked spasticity and Babinski)
  ▪ bowel, bladder incontinence, sexual dysfunction
  ▪ saddle anesthesia
  ▪ ataxia
  ▪ cord compression symptoms

• nerve root
  ▪ multiple peripheral nerve involvement
  ▪ radiculomyotomal/dermatomal deficits
  ▪ radiating back/neck pain

• peripheral nerve
  ▪ distal "stocking-glove distribution" sensory loss
  ▪ distal paresis
  ▪ LMN signs (hypotonia, hyporeflexia, fasciculations, atrophy)

• neuromuscular junction
  ▪ fluctuating ocular and proximal muscle weakness
  ▪ fatigable upgaze and diplopia
  ▪ bulbar involvement (bulbar symptoms)
  ▪ dysphonia, dysarthria

• muscle
  ▪ symmetric proximal weakness without sensory deficits +/-(climbing stairs, up from chair, combing hair)
  ▪ muscle tenderness
  ▪ muscle atrophy

### Differential Diagnosis

- vascular: ischemia, hemorrhage, vasculitis (temporal arteritis), aneurysm, vasospasm, hemato logic, embolic, thrombotic
- infectious/post-infectious: meningitis, encephalitis, sinus, osteomyelitis, abscess; viral, (herpes simplex, HIV, JC, polio, rabies), bacterial, (meningococcal, Lyme, botulism), mycobacterial (TB), spirochete (syphilis), parasitic, (cytisocercosis), protozoal, mycobacterial, (malaria), fungal, spirochete, (histoplasmosis, cryptococcus), prion, (CJD), post-infectious (GBS)
- neoplastic/paraneoplastic: metastatic (breast, lung, kidney, lymphoma, melanoma, kidney, breast) or primary (glioblastoma multiforme, meningioma, schwannoma, primary CNS lymphoma)
- paraneoplastic: small cell lung carcinoma, testicular, breast, gastrointestinal, ovarian
- degenerative: AD, ALS, FTD, HD, PD, PSP
- demyelinating: MS, GBS
- drugs: Alzheimer's, Parkinson's, ALS, medications/drugs, (anticholinergics, opiates, sedatives, chemotherapy), substance use/exposure (stimulants, hallucinogens, EtOH, heavy metals, carbon monoxide), withdrawal, pernicious anemia (levodopa, benzodiazepine)
- deficiencies: thiamine, niacin, pyridoxine (B6), vitamin B12, vitamin D, vitamin E
- inflammatory/auto-immune: polymyositis, myasthenia gravis, GBS, MS, dermatomyositis, MG, post-radiation therapy, granulomatous, collagen vascular, auto-immune
- ictal: epilepsy
- congenital/hereditary: hydrocephalus, cerebral palsy, fragile X syndrome
- anatomic/structural: ICP, cauda equina syndrome, herniation, HTN, decreased pressure (tonsillar, disc), Arnold-Chiari malformation, space-occupying lesion: tumour, pus, blood
- autoimmune
- traumatic: concussion, vertebral fracture, SDH, SAH, epidural hemorrhage
- endocrine/metabolic: DM, cirrhosis, hypoglycemia, uremia, hepatic encephalopathy, hypercapnia, thyroid, electrolyte, liver function test abnormality, endocrine, enzyme defect/ deposition (lysosomal and other), (Na⁺, K⁺, Ca²⁺, Mg²⁺), mitochondrial, nutrient deficiency
- toxic: medications/drugs, toxins, withdrawal
- movement disorder (dystonia, dyskinesia)
- sleep disorder
- ictal
- sleep: obstructive sleep apnea, restless leg syndrome, narcolepsy
- psychiatric
- psychiatric: depression, schizophrenia, anxiety, psychosomatic, malingering, pseudoseizure
- idiopathic
The Neurological Exam

General Exam and Mental Status

- **vitals:** pulse (especially rhythm), BP, RR, temperature
- **H&N:** meninges, head injury/bruises (signs of basal skull fracture: Battle’s sign, raccoon eyes, hemotympanum, CSF rhinorrhea/otorrhea), tongue biting
- **CVS:** carotid bruises, heart murmurs
- **mental status:** orientation (person, place, time), LOC (GCS) (see Emergency Medicine, ER4)
  - GCS/15 – Motor/6, Verbal/5 (T= intubated), Eyes/4
- **cognition**
  - Folstein MMSE – /30 (note: dementia is a clinical diagnosis and is not diagnosed by cognitive testing)
  - MoCA – /30 (≥26 is considered normal)
  - frontal lobe testing (for perseveration)
  - clock drawing

Cranial Nerve Exam

- **olfactory (CN I):** odour sensation (test each nostril separately)
- **optic (CN II)**
  1. visual acuity: test each eye individually using best corrected vision
  2. visual fields by confrontation
  3. pupil: direct and consensual pupillary reaction (affecter limb), accommodation, swinging flashlight test (see Relative Afferent Pupillary Defect, Ophthalmology; OP33)
  4. fundoscopy: optic disc edema, optic disc pallor, venous pulsations, hemorrhages
- **oculomotor (CN III), trochlear (CN IV), and abducens (CN VI)**
  1. oculomotor (CN III): levator palpebrae superioris, medial rectus, superior rectus, inferior rectus, inferior oblique, efferent limb of pupillary light response
  2. trochlear (CN IV): superior oblique
  3. abducens (CN VI): lateral rectus
- **trigeminal (CN V)**
  1. sensory: V1 (above supraorbital ridge), V2 (buccal area), V3 (mandible), corneal reflex (affecter)
  2. motor: temporalis, masseter, pterygoids, jaw jerk reflex
- **facial (CN VII)**
  1. inspect for facial asymmetry, widening of palpebral fissure, flattened nasolabial fold, drooping mouth, and involuntary facial movements
  2. sensorimotor: muscles of facial expression, hyperacusis (stapedius), corneal reflex (efferent)
  3. visceral sensory: taste of anterior 2/3 of tongue
  4. visceral motor: salivary and lacrimal glands
- **vestibulocochlear (CN VIII)**
  1. vestibular: nystagmus, caloric reflexes
  2. cochlear: whisper, Rinne, Weber
- **glossopharyngeal (CN IX) and vagus (CN X):** palatal elevation, gag reflex, vocal cord function, swallowing, taste of posterior third of tongue
- **accessory (CN XI):** trapezius and sternocleidomastoid strength
- **hypoglossal (CN XII):** tongue muscle bulk, fasciculations, strength

Motor Exam

- **bulk:** atrophy, asymmetry
- **tone:** hypotonia (flaccid), hypertonia (spasticity, rigidity, paratonia), cogwheeling
- **power:** pronator drift, asymmetric forearm rolling test
- **reflexes:** deep tendon reflexes, abdominal reflexes, primitive reflexes, Babinski, Hoffmann, clonus
- **abnormal movements:** tremors, chorea, dystonia, dyskinesia, hemiballism, myoclonus, athetosis, tics, fasciculations
- **abnormal posturing:** decorticate (flexion upper extremities, extension lower extremities), decerebrate (extension)

See Online Atlas for Cranial Nerves Exam, Motor Exam, and Sensory Exam Techniques

Battle’s sign = mastoid ecchymosis
Raccoon eyes = periorbital ecchymosis
If patient has not brought their glasses, have them look through a pinhole for best corrected vision
When testing CN I, avoid noxious smells like ammonia, as this tests CN V
Screening Neurologic Exam
- mental status: orientation (person, place, time), obeys commands, GCS
- head and neck: examine for lacerations, contusions, deformities, signs of basal skull fracture (periortbital or mastoid ecchymosis, ota/rhinorrhea), flex neck for meningismus if c-spine injury has been ruled out
- cranial nerve exam: visual fields ± fundoscopy, pupil size and reactivity, extraocular movements, facial strength, hearing to finger rub
- motor: power in deltoids, triceps, wrist extensors, hand interossei, iliopsoas, hamstrings, ankle dorsiflexors, pronator drift
- coordination: finger tapping, finger-to-nose, heel-knee-shin
- gait: tandem gait, heel walking
- reflexes: plantar, biceps, triceps, patellar, ankle
- sensation: all 4 limbs, including double simultaneous stimulation, vibration sense at great toes

CN Innervation of EOM
LR: CN VI, SD: CN IV, Other: CN III

Contraction of the left sternocleidomastoid turns the head right

Caloric: Brainstem Test
Describe nystagmus by direction of fast component
COWS
Cold
Opposite
Warm
Same
### Table 1. Localization of Motor Deficits

<table>
<thead>
<tr>
<th>Root/Muscle</th>
<th>LMN</th>
<th>UMN</th>
<th>Extrapyramidal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flaccid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasciculations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down-going (flexor)</td>
<td></td>
<td></td>
<td>Down-going (flexor)</td>
</tr>
<tr>
<td>Up-going (extensor, i.e. Babinski sign)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal, distal, or focal</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Flaccid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spastic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rigid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasciculations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyramidal pattern: look for hemiparetic gait (flexed arm, extended legs)</td>
<td></td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Upper extremities: extendors weaker than flexors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lower extremities: flexors weaker than extendors</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. Overview of Neuromuscular Diseases

<table>
<thead>
<tr>
<th>signs and symptoms</th>
<th>upper and lower motor neuron disease</th>
<th>peripheral neuropathy</th>
<th>neuromuscular junction</th>
<th>myopathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>weakness</td>
<td>segmental and asymmetrical, distal → proximal</td>
<td>distal (except GBS but may be asymmetrical</td>
<td>proximal and fatigable (e.g. MG, or weak then recovers (e.g. LEMS)</td>
<td>proximal</td>
</tr>
<tr>
<td>fasciculations</td>
<td>yes</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>reflexes</td>
<td>increased</td>
<td>decreased/absent</td>
<td>normal</td>
<td>normal (until late)</td>
</tr>
<tr>
<td>sensory</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
<tr>
<td>autonomic*</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
</tr>
</tbody>
</table>

### Table 3. Approach to Strength Testing of Radiculopathies vs. Peripheral Neuropathies

#### How to use this table: For each nerve root, learn two (or more) peripheral nerves (and their associated muscles/movements). In radiculopathies, all associated peripheral nerves (and their movements) will be impaired, whereas in peripheral neuropathies, only one of the nerves (and its movement) will be impaired, sparing the other nerves. Particularly useful peripheral nerve “pairs” are bolded for emphasis.

<table>
<thead>
<tr>
<th>root/nerve</th>
<th>movement</th>
<th>muscle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5</td>
<td>Axillary</td>
<td>Shoulder abduction</td>
</tr>
<tr>
<td>C6</td>
<td>Musculocutaneous (C5/6)</td>
<td>Elbow flexion</td>
</tr>
<tr>
<td></td>
<td>Radial (C6)</td>
<td>Elbow flexion</td>
</tr>
<tr>
<td></td>
<td>Wrist extension</td>
<td>Finger extension</td>
</tr>
<tr>
<td>C7</td>
<td>Radial</td>
<td>Elbow extension</td>
</tr>
<tr>
<td></td>
<td>Posterior interosseus</td>
<td>Finger extension</td>
</tr>
<tr>
<td>C8, T1</td>
<td>Median</td>
<td>Thumb flexion</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thumb abduction</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Opposition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Finger abduction</td>
</tr>
<tr>
<td>L2, 3, 4</td>
<td>Femoral Obturator</td>
<td>Hip flexion</td>
</tr>
<tr>
<td>L3, 4</td>
<td>Femoral (L3/4)</td>
<td>Knee extension</td>
</tr>
<tr>
<td></td>
<td>Deep peroneal (L4/5)</td>
<td>Duraflexion</td>
</tr>
<tr>
<td>L5</td>
<td>Sciatic (L5, S1)</td>
<td>Hip extension</td>
</tr>
<tr>
<td></td>
<td>Tibial</td>
<td>Ankle inversion</td>
</tr>
<tr>
<td></td>
<td>Superficial peroneal</td>
<td>Ankle eversion</td>
</tr>
<tr>
<td></td>
<td>Deep peroneal</td>
<td>Big toe extension</td>
</tr>
<tr>
<td>S1</td>
<td>Sciatic</td>
<td>Knee flexion</td>
</tr>
<tr>
<td></td>
<td>Tibial</td>
<td>Plantar flexion</td>
</tr>
</tbody>
</table>

### Upper Motor Neuron Tests

- **Babinski Reflex**: ‘Up-going’ big toe ± fanning of toes indicates an UMN lesion
- **Hoffman’s Reflex**: Flexion of IP joint of the thumb when tapping/flicking/flexing the nail of the index or ring finger may indicate an UMN lesion if asymmetrical
- **Pronator Drift**: Unable to maintain full arm extension and supination; side of forearm pronation reflects contralateral pyramidal tract lesion; closing eyes accentuates effect

### Pyramidal Pattern of Muscle Weakness (i.e. UMN)

- Weaker arm extendors: shoulder abduction, elbow extension, wrist extension, finger extension, finger abduction
- Weaker leg flexors: hip flexion, knee flexion, ankle dorsiflexion

### MRC Muscle Strength Scale

- 5 Full power
- 4 Submaximal power against resistance (ranging 4+, 4, 4-)
- 3 Full ROM against gravity without resistance
- 2 Full ROM with gravity removed
- 1 Muscle flicker
- 0 No muscle contraction

### Primitive Reflexes

- Grasp, palmomental, root, glabellar tap, snout

### Deep Tendon Reflexes

<table>
<thead>
<tr>
<th>root/muscle</th>
<th>deep tendon reflexes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C5/6</td>
<td>Biceps, Brachioradialis</td>
</tr>
<tr>
<td>C6</td>
<td>Triceps</td>
</tr>
<tr>
<td>C8</td>
<td>Finger flexors</td>
</tr>
<tr>
<td>L2/3</td>
<td>Hip adductors</td>
</tr>
<tr>
<td>L3/4</td>
<td>Knee extensors</td>
</tr>
<tr>
<td>S1/2</td>
<td>Plantar flexion</td>
</tr>
</tbody>
</table>

### Deep Tendon Reflex Scoring

- 0 Absent
- 1+ Depressed
- 2+ Normal
- 3+ Increased
- 4+ Clonus (≥4 beats)

### Interpreting a Slow or Uncoordinated Rapid Alternating Movement (RAM)

- Slow RMAs without fatiguing is suggestive of weakness (especially if it is asymmetric)
- Slow RMAs with fatiguing (i.e. decreasing amplitude over time) is suggestive of Parkinsonism
- Uncoordinated RAM is suggestive of cerebellar disorder (i.e. ataxia and irregularly irregular rhythm) or ideomotor apraxia
Sensory Exam

- primary sensation
  - spinothalamic tract: crude touch, pain, temperature
  - dorsal column-medial lemniscus pathway: fine touch, vibration, proprioception
- cortical sensation
  - graphesthesia, stereognosis, extinction, 2-point discrimination

Coordination Exam and Gait

- coordination exam
  - finger-to-nose, heel-to-shin, rapid alternating movements
- stance and gait
  - gait: antalgic, hemiplegic, ataxic, apraxic, festinating, foot drop, broad-based
  - tandem gait (heel-to-toe walking)
  - Romberg test
  - pull test for postural instability

Basic Anatomy Review

![Medulla](image1.png)
![Pons](image2.png)
![Midbrain](image3.png)

**Common Cerebellar Findings**
Frontal executive dysfunction/disinhibition, scanning speech, nystagmus, hypo- or hypermetric saccades, hypotonia, pendular reflexes, terminal tremor, ataxic finger-nose/heel-shin/tandem, wide based stance, positive rebound

**Romberg Test**
Stable with eyes open and closed = normal
Stable with eyes open, falls with eyes closed = positive Romberg, suggesting loss of joint position sense

![Figure 1. Brainstem (axial view)](image1.png)

![Figure 2. Brainstem (posterior view)](image2.png)
Figure 3. Discriminative touch pathway (dorsal column) from body

Figure 4. Spinothalamic tract from body

Figure 5. Discriminative touch pathway (dorsal column) from face

Figure 6. Spinothalamic tract pathway from face

Figure 7. Corticospinal motor pathway
Figure 8. Sympathetic and parasympathetic pathway

Figure 9. Dermatome map

Myotomes
C5 – Shoulder abduction/elbow flexion
C6 – Wrist extensors
C7 – Elbow extension
C8 – Squeeze hand
T1 – Finger abduction
T2-9 – Intercostal (abdominal reflexes)
T9-10 – Upper abdominals
T11-12 – Lower abdominals
L2 – Hip flexion
L3 – Hip adduction
L4 – Knee extension and ankle dorsiflexion
L5 – Ankle dorsiflexion and big toe extension
S1 – Plantarflexion
Lumbar Puncture

Indications
• diagnostic: CNS infection (meningitis, encephalitis), inflammatory disorder (MS, Guillain-Barré, vasculitis), subarachnoid hemorrhage (if CT negative), CNS neoplasm (neoplastic meningitis)
• therapeutic: to administer anesthesia, chemotherapy, contrast media; to decrease ICP (pseudotumor cerebri, NPH)

Contraindications
• mass lesion causing increased ICP, could lead to cerebral herniation; CT first if suspect mass lesion
• infection over LP site/suspected epidural abscess
• low platelets (<50,000) or treatment with anticoagulation (high INR or aPTT)
• uncooperative patient

Complications
• tonsillar herniation (rare)
• SDH
• transient 6th nerve palsy
• post-LP headache (5-40%): worse when upright, better supine; generally onset within 24 h
• prevention: smaller gauge (i.e. 22) needle; reinsert stylet prior to needle removal, blunt-ended needle
• symptomatic treatment: caffeine and sodium benzoate injection
• corrective treatment: blood patch (autologous)
• spinal epidural hematoma
• infection

LP Tubes
• tube #1: cell count and differential: RBCs, WBCs, and differential
  • xanthochromia (yellow bilirubin pigmentation implies recent bleed into CSF, diagnostic of SAH)
• tube #2: chemistry: glucose (compare to serum glucose) and protein
• tube #3: microbiology: Gram stain and C&S
  • specific tests depending on clinical situation/suspicion
  • viral: PCR for herpes simplex virus (HSV) and other viruses
  • bacterial: polysaccharide antigens of H. influenzae, N. meningitidis, S. pneumoniae
  • fungal: cryptococcal antigen, culture
  • TB: acid-fast stain, TB culture, TB PCR
• tube #4: cytology: for evidence of malignant cells
• tube #5: cell count: compare RBC count to that of tube #1
  • note: tube 4 or 5 can be sent for repeat cell count

Table 4. Lumbar Puncture Interpretation (Normal vs. Various Infectious Causes)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Colour</th>
<th>Protein</th>
<th>Glucose</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>NORMAL</td>
<td>Clear</td>
<td>&lt;0.45 g/L</td>
<td>60% of serum glucose or &gt;3.0 mmol/L</td>
<td>0-5 x 10^6/L</td>
</tr>
<tr>
<td>INFECTIOUS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral Infection</td>
<td>Clear or opalescent</td>
<td>Normal or slightly increased</td>
<td>Normal</td>
<td>&lt;1,000 x 10^6/L Lymphocytes mostly, some PMNs</td>
</tr>
<tr>
<td>Bacterial Infection</td>
<td>Opalescent yellow, may clot</td>
<td>&gt;1 g/L</td>
<td>Decreased (&lt;25% serum glucose or &lt;2.0 mmol/L)</td>
<td>&gt;1,000 x 10^6/L PMNs</td>
</tr>
<tr>
<td>Granulomatous Infection (tuberculosis, fungal)</td>
<td>Clear or opalescent</td>
<td>Increased but usually &lt;5 g/L</td>
<td>Decreased (usually &lt;2.0-4.0 mmol/L)</td>
<td>&lt;1,000 x 10^6/L Lymphocytes</td>
</tr>
</tbody>
</table>

Approach to Common Presentations

Weakness

Approach
• mode of onset: abrupt (vascular, toxic, metabolic), subacute (neoplastic, infective, inflammatory), insidious (hereditary, degenerative, endocrine, neoplastic)
• course: worse at onset (vascular), progressive (neoplastic, degenerative, infective), episodic (vascular, inflammatory), activity dependent (NMJ, muscular)
• pattern: objective vs. subjective, generalized vs. localized, asymmetric vs. symmetric, proximal vs. distal, UMN vs. LMN, peripheral vs. myotomal
• associated symptoms: sensory symptoms, cortical symptoms, spinal symptoms (i.e. bowel/bladder dysfunction), signs/symptoms specific to various etiologies
• history: family history, developmental history, medications, risk factors, recent/preceding exposures
• investigations for LMN: NCS/EMG
• investigations for UMN: imaging (brain and/or spinal cord)
Differential Diagnosis
- objective muscle weakness; also, differentiate between true muscle weakness vs. fatigue
  - generalized
  - myopathy (proximal > distal weakness)
    - endocrine: hypothyroidism, hyperthyroidism, Cushing's syndrome
    - rheumatologic: polymyositis, vasculitis
    - infectious: HIV, CMV, influenza
    - other: collagen vascular disorders, steroids, statins, alcohol, electrolyte disorders
  - NMJ (MG, botulism, LEMS, organophosphate poisoning)
  - cachexia
  - localized
    - UMN (leukodystrophy, vasculitis, abscess, brain tumour, vitamin B₁₂ deficiency, MS, stroke)
    - radicular pain (i.e. nerve root)
    - anterior horn cell (spinal muscular atrophy, ALS, polio, paraneoplastic, lead toxicity)
    - peripheral neuropathy (peroneal muscle atrophy, GBS, leprosy, amyloid, myeloma, DM, lead toxicity)
- no objective muscle weakness
  - chronic illness (cardiac, pulmonary, anemia, infection, malignancy)
  - depression, deconditioning
- if loss of passive motion, consider intra-articular, peri-articular, or extra-articular causes

Numbness/Altered Sensation

Approach
- positive sensory symptoms: paresthesia/dysesthesia = tingling, pins and needles, prickling, burning, stabbing
- negative sensory symptoms: hypoesthesia/anesthesia = numbness, diminution, or absence of feeling
- determine distribution of sensory loss:
  - nerve root vs. peripheral nerve?
  - symmetric stocking-glove pattern? (indicative of distal symmetric polyneuropathy)
  - anterior-posterior spinal cord dissociation
- investigations: NCS, vitamin B₁₂ levels, imaging based on associated findings

Differential Diagnosis
- cerebral: stroke, demyelination, tumour
  - associated symptoms: hemiplegia, aphasia, apraxia
- brainstem: stroke, demyelination, tumour
  - associated symptoms: diplopia, vertigo, dysarthria, dysphagia
- spinal cord/radiculopathy: cord infarction, tumour, MS, syringomyelia, vitamin B₁₂ deficiency, disc lesion
  - associated symptoms: back/neck pain, weakness (paraparesis or Brown-Séquard pattern)
- neuropathy: local compressive neuropathy (based on location and distribution), DM, uremia, vasculitis, vitamin B₁₂ deficiency, HIV, Lyme disease, alcohol, paraneoplastic, amyloid

Cranial Nerve Deficits

CN I: Olfactory Nerve

Clinical Features
- absence of sense of smell associated with a loss of taste

Differential Diagnosis
- nasal: physical obstruction
  - heavy smoking, chronic rhinitis, sinusitis, neoplasms, septal deformity, choanal atresia, vestibular stenosis, foreign body
- olfactory neuroepithelial: destruction of receptors or their axon filaments
  - influenza, herpes simplex, interferon treatment of hepatitis C virus, atrophic rhinitis (leprosy)
- central: lesion of olfactory pathway
  - Kallmann syndrome, albinism, head injury, cranial surgery, SAH, chronic meningeval inflammation, meningioma, aneurysm, PD, stroke, MS
- endocrine/metabolic
  - DM, adrenal hypo/hyperfunction, pseudohypoparathyroidism, hypothyroidism, renal/liver failure, vitamin deficiency
CN II: Optic Nerve

Clinical Features
- palsy (depressed and abducted), pupil dilated (mydriasis)
- vertical and horizontal diplopia; paralysis of adduction, elevation, and depression

Differential Diagnosis
- PComm aneurysm: early mydriasis, then CN III palsy
- cavernous sinus (internal carotid aneurysm, meningioma, sinus thrombosis): associated with deficits in other CNs near the cavernous sinus
- ischemia of CN III (DM, temporal arteritis, HTN, atherosclerosis): pupil sparing CN III palsy
- midbrain lesion: complete unilateral CN III palsy with bilateral weakness of the superior rectus and ptosis with contralateral pyramidal signs ± mydriasis
- orbital lesion: associated with optic neuropathy, chemosis, proptosis
- other (inflammatory, infection, neoplasia, uncal herniation, trauma)

CN IV: Trochlear Nerve

Clinical Features
- vertical and torsional diplopia; defect of intorsion and depression
- patient may complain of difficulty going down stairs or reading

Differential Diagnosis
- common: ischemic (DM, HTN), idiopathic, trauma (TBI or surgical), congenital
- other: cavernous sinus lesion, superior orbital fissure (tumour, granuloma)

CN V: Trigeminal Nerve

Clinical Features
- ipsilateral facial numbness, weakness of muscles of mastication (V3 only) with ptymylogeal deviation towards the side of the lesion

Differential Diagnosis
- brainstem (ischemia, tumour, syringobulbia, demyelination)
- peripheral (tumour, aneurysm, chronic meningitis, metastatic infiltration of nerve)
- trigeminal ganglion (acoustic neuroma, meningioma, fracture of middle fossa)
- cavernous sinus (carotid aneurysm, meningioma, sinus thrombosis)
- trauma
- note: other CN V lesions that cause facial pain = trigeminal neuralgia, herpes zoster

CN VI: Abducens Nerve

Clinical Features
- resting inward deviation (esotropia)
- horizontal diplopia; defect of lateral gaze

CN IV is the only cranial nerve that crosses the midline and exits posteriorly
A CN IV lesion may cause a contralateral deficit
CN IV is at risk of trauma during neurosurgical procedures involving the midbrain because of its long intracranial course
Jaw deviation is towards the side of a LMN CN V lesion
CN VI has the longest intracranial course and is vulnerable to increased ICP, creating a false localizing sign
Differential Diagnosis
- pons (infarction, hemorrhage, demyelination, tumour): associated with facial weakness and contralateral pyramidal signs
- tentorial orifice (compression, meningioma, trauma): false localizing sign of increased ICP
- cavernous sinus (carotid aneurysm, meningioma, sinus thrombosis)
- ischemia of CN VI (DM, temporal arteritis, HTN, atherosclerosis)
- congenital (Duane’s syndrome)

CN VII: Facial Nerve

Clinical Features
- LMN lesion: ipsilateral facial weakness (facial droop, flattening of forehead, inability to close eyes, flattening of nasolabial fold)
- UMN lesion: contralateral facial weakness with forehead sparing (due to bilateral frontalis innervation)
- impaired lacrimation, decreased salivation, numbness behind auricle, hyperacusis, taste dysfunction of anterior 2/3 of tongue

Differential Diagnosis
- idiopathic = Bell’s palsy, 80-90% of cases (see Otolaryngology, OT23)
  - most often related to HSV, but other viruses may be implicated (CMV, herpes zoster, EBV)
- other: temporal bone fracture, EBV, Ramsay Hunt (HSV), otitis media/mastoiditis, sarcoidosis, DM mononeuropathy, parotid gland disease, Lyme meningitis, HIV

CN VIII: Vestibulocochlear Nerve

- see Otolaryngology, OT9

CN IX: Glossopharyngeal Nerve

Clinical Features
- unilateral lesion is rare
- taste dysfunction in posterior 1/3 of tongue
- absent gag reflex and dysphagia

Disorders
- glossopharyngeal neuralgia: sharp paroxysmal pain of posterior pharynx radiating to ear, triggered by swallowing
  - treated with carbamazepine or surgical ablation of CN IX

Differential Diagnosis of Lower Cranial Nerve Deficits (CN IX, X, XI, XII)
Intracranial/Skull Base: meningioma, neurolipoma, metastases, osteomyelitis, meningitis
Intracranial/Skull Base: meningioma, neurolipoma, metastases, osteomyelitis, meningitis
Neck: trauma, surgery, tumours

Normal swallowing is initiated when the tongue moves a bolus back into the palatal archway. Tongue movements are innervated exclusively by CN XII. The bolus stimulates the soft palate to elevate and the bolus is deflected into the oropharynx. Next the pharyngeal constrictors contract, the larynx elevates, and the vocal cords close. Swallowing depends on afferent information via CN V, IX, and X and motor action via CN V, VII, IX, X, and XII. Connections in the nucleus of the tractus solitarius in the medulla (in proximity to the respiratory centre) act as the swallowing centre. Swallowing and breathing are coordinated to prevent aspiration.
CN X: Vagus Nerve

Clinical Features
• oropharyngeal dysphagia (transfer dysphagia) due to palatal and pharyngeal weakness
  ▪ neuromuscular causes of dysphagia
    • CNS: stroke, cerebral palsy, tumour, trauma, PD, AD, MS
    • CN: DM, laryngeal nerve palsy, polio, ALS
    • myopathic/NMJ: dermatomyositis, polymyositis, MG, sarcoidosis
  ▪ other causes of dysphagia: see Gastroenterology, G8
• dysarthria: inability to produce understandable speech due to impaired phonation and/or resonance

CN XI: Accessory Nerve

Clinical Features
• LMN lesion: paralysis of ipsilateral trapezius and sternocleidomastoid (ipsilateral shoulder drop, weakness on turning head to contralateral side)
• UMN lesion: paralysis of ipsilateral sternocleidomastoid and contralateral trapezius

CN XII: Hypoglossal Nerve

Clinical Features
• LMN lesion: tongue deviation towards lesion; ipsilateral tongue atrophy and fasciculations (if chronic)
• UMN lesion: tongue deviation away from lesion; absence of atrophy and fasciculations

Table 5. Cranial Nerve Examination and Associated Deficits

<table>
<thead>
<tr>
<th>Cranial Nerve</th>
<th>Recommended Physical Exams</th>
<th>Signs/Symptoms of Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olfactory (CN I)</td>
<td>Odor sensation: test each nostril separately</td>
<td>Anosmia (should be associated with loss of taste)</td>
</tr>
<tr>
<td>Optic (CN II)</td>
<td>Visual acuity: test each eye individually; best corrected vision</td>
<td>Blindness</td>
</tr>
<tr>
<td>Oculomotor (CN III)</td>
<td>Test visual fields; Assess pupils: direct and consensual pupillary reaction (afferent), RAPD (swinging flashlight test); Fundoscopy: optic disc edema and pallor, venous pulsations, hemorrhages</td>
<td>Absence of light reflexes</td>
</tr>
<tr>
<td></td>
<td>Assess extraocular movements and nystagmus</td>
<td>Eyes deviated down and out; can demonstrate mydriasis</td>
</tr>
<tr>
<td></td>
<td>Test effenter limb of pupillary light response</td>
<td>Vertical diplopia; may tilt head towards unaffected side; affected eye cannot turn inward and downward</td>
</tr>
<tr>
<td></td>
<td>Test efferent limb of corneal reflex</td>
<td>Loss of facial sensations and corneal reflex on stimulation ipsilaterally</td>
</tr>
<tr>
<td></td>
<td>Test corneal reflex (afferent limb)</td>
<td>Weakness and wasting of muscles of mastication; deviation of open jaw to ipsilateral side; trigeminal neuralgia</td>
</tr>
<tr>
<td></td>
<td>Assess motor function: temporalis, masseter, pterygoids, jaw jerk reflex</td>
<td>Horizontal diplopia, esotropia (convergent strabismus) and abductor paralysis of ipsilateral eye</td>
</tr>
<tr>
<td></td>
<td>Test movement of superior oblique</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Test movement above supraorbital ridge (V1), buccal area (V2), mandible (V3)</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Test corneal reflex (afferent limb)</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Assess motor function: temporalis, masseter, pterygoids, jaw jerk reflex</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Test movement of lateral rectus</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Sensorimotor nerve function: to muscles of facial expression</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Test effenter limb of corneal reflex</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Visceral sensory nerve function: to anterior 2/3 of the tongue</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Visceral motor nerve function: to salivary and lacrimal glands</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Vestibulocochlear function (nystagmus, caloric)</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Cochlear function (Rinne, Weber)</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Assess vocal cord function and gag reflex</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Assess taste to posterior third of the tongue (bitter and sour taste)</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Assess vocal cord function and gag reflex</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Observe uvula deviation and palatal elevation</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Assess swallowing</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Assess strength of trapezius (shoulder shrug) and sternocleidomastoid muscles (head turn)</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
<tr>
<td></td>
<td>Inspect tongue for signs of lateral deviation, atrophy, fasciculations, asymmetry of movement and strength</td>
<td>Ipsilateral tongue paralysis with contralateral hemiparesis/sensory symptoms is pathognomonic for a spinal medullary infarction</td>
</tr>
</tbody>
</table>
NEURO-OPHTHALMOLOGY

Abnormalities of Vision

• see Ophthalmology, OP4

Acute Visual Loss

• see Ophthalmology, OP4

Optic Neuritis

• see Optic Disc Edema below, Multiple Sclerosis, N54

Anterior Ischemic Optic Neuropathy

• see Optic Disc Edema, below
• non-arteritic (NAION): due to atherosclerosis
• arteritic (AION): due to giant cell arteritis (see Rheumatology, RH20)

Amaurosis Fugax

• see Ophthalmology, OP37 and Stroke, N50

Central Retinal Vein Occlusion

• see Ophthalmology, OP24

Optic Disc Edema

Table 6. Common Causes of Optic Disc Edema

<table>
<thead>
<tr>
<th>Age</th>
<th>Vision</th>
<th>Symptoms</th>
<th>Pupil</th>
<th>Fundus</th>
<th>Etiologies</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 yr</td>
<td>Rapidly progressive</td>
<td>Pain (especially with eye movement)</td>
<td>RAPD</td>
<td>Disc swelling if anterior disc</td>
<td>MS, viral</td>
<td>MRI with gadolinium</td>
<td>IV methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>monocular central vision loss with visual acuity and colour vision with recovery</td>
<td>H/A, N/V, local neurological deficits</td>
<td>No RAPD</td>
<td>Bilateral disc swelling, retinal hemorrhage, no venous pulsations</td>
<td>Increased ICP</td>
<td>Emergent CT: LP if CT is normal to measure opening pressure</td>
<td>Treat cause</td>
</tr>
<tr>
<td>&gt;50 yr but usually &gt;70 yr</td>
<td>Late visual loss</td>
<td>If GCA: H/A, scalp tenderness, jaw claudication, weight loss, fatigue</td>
<td>RAPD</td>
<td>Pale segmental disc edema, retinal dot, flame hemorrhages</td>
<td>Giant cell arteritis</td>
<td>CBC, ESR, CRP, temporal artery biopsy</td>
<td>Consider ASA if non-arteritic; steroids if arteritic</td>
</tr>
<tr>
<td>&gt;50 yr</td>
<td>Painless unilateral acute field defect over hours to days with colour vision</td>
<td>Painless unilateral variable vision loss</td>
<td>± RAPD</td>
<td>Swollen disc, venous engorgement, retinal hemorrhage</td>
<td>Non-arteritic: atherosclerosis</td>
<td>Fluorescein angiogram and coherence tomography</td>
<td>Optimize risk factors, reduce IOP, ± laser, ± VEGF inhibitors</td>
</tr>
</tbody>
</table>

NAION can be caused by use of sildenafil (Viagra®) in rare cases

If you suspect the diagnosis of giant cell arteritis do not wait for biopsy results. Begin treatment immediately

NAION can be caused by use of sildenafil (Viagra®) in rare cases
**Optic Disc Atrophy**

- **etiologies:** glaucoma, AION, compressive tumour, optic neuritis, Leber’s hereditary optic neuropathy, congenital
- **presentation:** disc pallor, low visual acuity, peripheral vision defect, decreased colour vision
- **treatment:** none (irreversible), aim to prevent

**Abnormalities of Visual Field**

**Visual Fields Defects**

- Right anopsia (right optic nerve lesion)
- Right anopsia and left upper quadrantanopsia (junctional scotoma)
- Bitemporal hemianopsia (chiasmal lesion)
- Left homonymous hemianopsia (right optic tract lesion)
- Left upper quadrantanopsia (right temporal lesion)
- Left lower quadrantanopsia (right parietal lesion)

**Figure 13. Characteristic visual field defects with lesions along the visual pathway**

**Abnormalities of Eye Movements**

**Disorders of Gaze**

**Pathophysiology**

- horizontal gaze: FEF → contralateral PPRF (midbrain/pons) → eyes saccade away from FEF
- vertical gaze: cortex → rostral interstitial nucleus in the MLF (midbrain)

**Clinical Features**

- unilateral lesion in one FEF → eyes deviate toward the side of the lesion
  - can be overcome with doll’s eye maneuver
- unilateral lesion in the PPRF → eyes deviate away from the lesion
  - cannot be overcome with doll’s eye maneuver if CN VI nucleus lesion as well
- seizure involving a FEF: eyes deviate away from the focus

**Etiology**

- common: infarcts (frontal or brainstem), MS, tumours

**Internuclear Ophthalmoplegia**

**Pathophysiology**

- results from a lesion in MLF which disrupts coordination between CN VI nucleus in pons and the contralateral CN III nucleus in midbrain → disrupts conjugate horizontal gaze

**Clinical Features**

- horizontal diplopia on lateral gaze, oscillopsia
- on gaze away from the side of the lesion
  - ipsilateral adduction defect
  - contralateral abduction nystagmus
- cannot be overcome by caloric testing
- accommodation reflex intact
- may be bilateral (especially in MS)

**Etiology**

- common: MS, brain stem infarct

**Investigations**

- MRI
Diplopia

Etiology – Monocular (see Ophthalmology, OP7)
- mostly due to relatively benign optical problems (refractive error, cataract) or functional

Etiology – Binocular (due to ocular misalignment)
- muscle
  - Graves’ ophthalmopathy
  - EOM restriction/entrapment
- neuromuscular junction
  - MG (see Myasthenia Gravis, N40)
- cranial nerve palsy (see Cranial Nerve Deficits, N10)
- INO (see Internuclear Ophthalmoplegia, N15)
- other
  - orbital trauma (orbital floor fracture), tumour, infection, inflammation
  - Miller-Fisher variant of GBS
  - Wernicke’s encephalopathy
  - leptomeningeal disease

Approach to Diplopia
- monocular vs. binocular
- horizontal vs. vertical vs. oblique diplopia
- direction of gaze that exacerbates diplopia
- corrective head movements

Workup
- may observe isolated 4th or 6th nerve palsy for a few weeks, but workup if persistent or other symptoms develop
- indications for neuroimaging
  - bilateral or multiple nerve involvement
  - severe sudden onset headache (rule out aneurysm)

Nystagmus

- definition: rapid, involuntary, small amplitude movements of the eyes that are rhythmic in nature
- direction of nystagmus is labelled by the rapid component of the eye movement
- can be categorized by movement type (pendular, jerking, rotatory, coarse) or as physiological vs. pathological

Table 7. Nystagmus Features

<table>
<thead>
<tr>
<th></th>
<th>Peripheral (Vestibular)</th>
<th>Central (Brainstem)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Direction</td>
<td>Unidirectional, fast phase away from the lesion</td>
<td>May be bilateral/unidirectional</td>
</tr>
<tr>
<td>Vertical Nystagmus</td>
<td>–</td>
<td>±</td>
</tr>
<tr>
<td>Gaze Fixation</td>
<td>Relieves nystagmus</td>
<td>Does not relieve nystagmus</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Severe</td>
<td>Mild</td>
</tr>
<tr>
<td>Auditory Symptoms</td>
<td>Common</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Other Neurological Signs</td>
<td>Absent</td>
<td>Often present</td>
</tr>
<tr>
<td>DDx</td>
<td>Benign paroxysmal positional vertigo, vestibular neuritis, Ménière’s disease, toxicity, trauma, Ramsay Hunt syndrome</td>
<td>MS, vascular (brainstem/cerebellar), neoplastic/paraneoplastic</td>
</tr>
</tbody>
</table>

Abnormalities of Pupils

- see Ophthalmology, OP30
Nutritional Deficiencies and Toxic Injuries

- sufficient nutritional intake is required for optimal nervous system functioning; deficiencies in the following key nutrients, among others, may impair central and peripheral nervous system function (potential neurological symptoms are provided)

Table 8. Nutritional Deficiency Features and Management

<table>
<thead>
<tr>
<th>Vitamin Deficiency</th>
<th>Neurological Clinical Manifestation</th>
<th>Investigation</th>
<th>Treatment*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vitamin B₁₂</strong></td>
<td>Paresthesias and a sensory ataxia are the most common initial symptoms; Myelopathy; may be accompanied by peripheral neuropathy; Neuropsychiatric manifestations: memory impairment, change in personality, delirium, and psychosis; Optic neuropathy</td>
<td>Serum cobalamin; Serum methylmalonic acid; Serum homocysteine</td>
<td>IM Vitamin B₁₂ 1,000 μg for 5 d, then once per month or oral B₁₂ 1,000 μg/d</td>
</tr>
<tr>
<td><strong>Folate</strong></td>
<td>Myelopathy, peripheral neuropathy; May be clinically indistinguishable from Vitamin B₁₂ deficiency</td>
<td>Serum folate; Homocysteine</td>
<td>Oral folate 1 mg tid initially; 1 mg daily thereafter</td>
</tr>
<tr>
<td><strong>Copper</strong></td>
<td>Myelopathy, pyramidal signs (e.g. brisk muscle stretch reflexes at the knees and extensor plantar responses); Severe sensory loss</td>
<td>Serum copper and ceruloplasmin; urinary copper</td>
<td>Discontinue zinc; oral copper 8 mg/d for 1 wk; 6 mg/d for 1 wk; 4 mg/d for 1 wk; 2 mg/d thereafter</td>
</tr>
<tr>
<td><strong>Vitamin E</strong></td>
<td>Ophthalmoplegia, retinopathy, spinocerebellar syndrome with peripheral neuropathy (with signs of cerebellar ataxia); Severe sensory loss</td>
<td>Serum vitamin E; ratio serum vitamin E to sum of cholesterol and triglycerides</td>
<td>Vitamin E 2,200 mg/kg/d oral or IM</td>
</tr>
<tr>
<td><strong>Thiamine</strong></td>
<td>Three well-described manifestations include: beriberi (dry and wet); infantile beriberi; Wernicke’s encephalopathy with Korsakoff’s syndrome; Alcoholism is a cause of reduced intake of thiamine, leading to deficiency</td>
<td>Clinical diagnosis; brain MRI</td>
<td>Thiamine 100 mg IV followed by 50-100 mg IV or IM until nutritional status stable</td>
</tr>
<tr>
<td><strong>Pyridoxine</strong> (Vitamin B₆)</td>
<td>Painful sensorimotor peripheral neuropathy</td>
<td>Serum pyridoxal phosphate</td>
<td>Pyridoxine 50-100 mg daily</td>
</tr>
<tr>
<td><strong>Niacin</strong></td>
<td>Encephalopathy, coma, and peripheral neuropathy</td>
<td>Urinary excretion niacin metabolites</td>
<td>Nicotinic acid 25-50 mg daily oral or IM</td>
</tr>
</tbody>
</table>

*IM = intramuscular; IV = intravenous

- it is also important to consider occupational neurotoxic syndromes secondary to exposure to pesticides, solvents, and metals. Encephalopathy, extrapyramidal features, neurodegenerative diseases, and peripheral neuropathy are commonly encountered. Onset and progression of neurological diseases should be temporally related to neurotoxin exposure. Main toxins associated with neurotoxicity are listed below

Table 9. Selected Occupational Neurotoxic Syndromes

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Associated Occupations</th>
<th>Characteristic Neurological Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organic solvents</strong></td>
<td>Printer, spray painters, industrial cleaners, paint or glue manufacturers, graphic industry, electronic industry, plastic industry</td>
<td>Nausea, H/A, concentration difficulty; Long-term exposure may lead to “chronic solvent-induced encephalopathy”, characterized by mild-to-severe cognitive impairment</td>
</tr>
<tr>
<td><strong>Pesticides (e.g. insecticides, fungicides, rodenticides, fumigants, herbicides)</strong></td>
<td>Agricultural work, pesticide manufacturing and formulating employees, highway and railway workers, green house, forestry and nursery workers</td>
<td>Parkinson’s disease risk increased by —70% following pesticide exposure</td>
</tr>
<tr>
<td><strong>Metals (e.g. lead, mercury, manganese, aluminum, arsenic)</strong></td>
<td>Battery and metal production (e.g. soldier, pipes), chemical and electronic application industries, steel manufacturing, welders, alloy workers, transportation, packaging, construction</td>
<td>Lead: delayed or reversed development, permanent learning disabilities, seizures, coma, death from encephalopathy (rare); Mercury: psychiatric disturbances, ataxia, visual loss, hearing loss, tiredness, memory disturbances; Manganese: psychiatric symptoms, hallucinations (“manganese madness”), extrapyramidal features, dystonia, parkinsonism (manganism); Aluminum: implicated in Alzheimer’s pathogenesis; Arsenic: sleeplessness/sleepiness, irritability, H/A, spasms in muscle extremities and muscle fatigue</td>
</tr>
<tr>
<td><strong>Gases (e.g. carbon dioxide, nitrous oxide, formaldehyde)</strong></td>
<td>Anesthesia, disinfection, manufacture of illuminating gas and water-gas</td>
<td>Cognitive/behavioural and emotional symptoms, parkinsonian syndromes</td>
</tr>
</tbody>
</table>

Neurologic Complications due to Toxic Injuries Related to Bariatric Surgery

- deficiencies of both fat- and water-soluble vitamins may occur following malabsorptive bariatric surgery
- patients who have undergone malabsorptive surgery should be monitored for late metabolic complications and neurological manifestations
Seizure Disorders and Epilepsy

Seizure

Definitions
- seizure: transient neurological dysfunction caused by excessive activity of cortical neurons, resulting in paroxysmal alteration of behaviour and/or EEG changes
- epilepsy: chronic condition characterized by two or more unprovoked seizures

Classification

Seizure

Unprovoked

Partial

Can secondarily become

Generalized

Provoked

Fever

Metabolic Trauma

Unprovoked Provoked

Absence

Clonic

Tonic

Tonic-Clonic

Myoclonic

Atonic

Motor

Sensory

Autonomic

Psychiatric

Non-Convulsive

Convulsive

Simple

Complex

Figure 16. Classification of seizures

NOTE: seizures can also be classified using age of onset (childhood/adolescence, adulthood/late [i.e. > age 30]), setting (sleep, upon awakening), EEG (focal, generalized)

Signs and Symptoms
- partial seizures
  - simple or complex can secondarily generalize, or simple → complex → generalized seizures
  - simple (preserved LOC)
    - motor: postural, phonatory, forceful turning of eyes and/or head, focal muscle rigidity/jerking ± Jacksonian march (spreading to adjacent muscle groups)
    - sensory: unusual sensations affecting vision, hearing, smell, taste, or touch
    - autonomic: epigastric discomfort, pallor, sweating, flushing, piloerection, pupillary dilatation
    - psychiatric: symptoms rarely occur without impairment of consciousness and are more commonly complex partial
  - complex (altered LOC)
    - patient may appear to be awake but with impairment of awareness
    - classic complex seizure is characterized by automatisms such as chewing, swallowing, lip-smacking, scratching, fumbling, running, disrobing, and other stereotypic movements
    - other forms: dysphasic, dysmnesic (déjà vu), cognitive (disorientation of time sense), affective (fear, anger), illusions, structured hallucinations (music, scenes, taste, smells), epigastric fullness
- generalized seizures (decreased LOC)
  - absence (petit mal): usually only seen in children, unresponsive for 5-10 s with arrest of activity, staring, blinking or eye-rolling, no post-ictal confusion; 3 Hz spike and slow wave activity on EEG
  - clonic: repetitive rhythmic jerking movements
  - tonic: muscle rigidity in flexion or extension
  - tonic-clonic (grand mal, generalized tonic-clonic [GTC])
    - prodrome of unease or irritability hours to days before the episode
    - tonic ictal phase: muscle rigidity
    - clonic ictal phase: repetitive violent jerking of face and limbs, tongue biting, cyanosis, frothing, incontinence
    - post-ictal phase: flaccid limbs, extensor plantar reflexes, headache, confusion, aching muscles, sore tongue, amnesia, elevated serum CK lasting hours
  - myoclonic: sporadic contractions localized to muscle groups of one or more extremities
  - atonic: loss of muscle tone leading to drop attack

Temporal lobe epilepsy is suggested by an aura of fear, olfactory or gustatory hallucinations, and visceral or déjà vu sensations

Frontoparietal cortex seizures are suggested by contralateral focal sensory or motor phenomena

Stroke is the most common cause of late-onset (>50 yr) seizures, accounting for 50-80% of cases

Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia

Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia

Neurodegenerative diseases can underlie seizures; conversely, seizures can be a cause of dementia
Table 10. Classic Factors Differentiating Seizure vs. Syncope

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time of Onset</td>
<td>Day or night</td>
<td>Day</td>
</tr>
<tr>
<td>Position</td>
<td>Any</td>
<td>Upright, not recumbent</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden or brief</td>
<td>Gradual</td>
</tr>
<tr>
<td>Aura</td>
<td>Possible specific aura</td>
<td>Lightheaded sensation</td>
</tr>
<tr>
<td>Colour</td>
<td>Normal or cyanotic</td>
<td>Pallor</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Uncommon outside of ictal phase</td>
<td>Common; diaphoresis</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief or prolonged</td>
<td>Brief</td>
</tr>
<tr>
<td>Incontinence</td>
<td>Common</td>
<td>Possible but rare</td>
</tr>
<tr>
<td>Post-Ictal</td>
<td>Occurs in tonic-clonic or complex partial</td>
<td>No</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>Common</td>
<td>Occasional brief jerks</td>
</tr>
<tr>
<td>Injury</td>
<td>Common, tongue biting</td>
<td>Rare unless from fall</td>
</tr>
<tr>
<td>Automatisms</td>
<td>Common in absence or complex partial</td>
<td>None</td>
</tr>
<tr>
<td>EEG</td>
<td>Usually abnormal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Table 11. Classic Factors Differentiating Seizure vs. Pseudoseizure (Conversion Disorder)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Seizure</th>
<th>Pseudoseizure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triggers</td>
<td>Uncommon</td>
<td>Emotional disturbance</td>
</tr>
<tr>
<td>Duration</td>
<td>Brief or prolonged</td>
<td>May be prolonged</td>
</tr>
<tr>
<td>Motor Activity</td>
<td>Synchronous, stereotypic, automatisms, lateral tongue biting, eyes rolled back</td>
<td>Opisthotonus, rigidity, forced eye closure, irregular extremity movements, shaking head, pelvic thrust, crying, geotropic eye movements, tongue biting at the tip</td>
</tr>
<tr>
<td>Timing</td>
<td>Day or night</td>
<td>Day; other people present</td>
</tr>
<tr>
<td>Physical Injury</td>
<td>May occur</td>
<td>Rare</td>
</tr>
<tr>
<td>Incontinence</td>
<td>May occur</td>
<td>Rare</td>
</tr>
<tr>
<td>Reproduction of Attack</td>
<td>Spontaneous</td>
<td>Suggestion ± stimulus</td>
</tr>
<tr>
<td>EEG</td>
<td>Often inter-ictal discharges</td>
<td>Normal</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

*Pseudoseizures do not rule out seizures (not uncommon to present with both)

- Alcoholic withdrawal seizures may occur up to 2 days from the last exposure to alcohol (see Emergency Medicine, ER54)

**Investigations**
- CBC, electrolytes, fasting blood glucose, Ca²⁺, Mg²⁺, ESR, Cr, liver enzymes, CK, prolactin
- Also consider toxicology screen, EtOH level, AED level (if applicable)
- CT/MRI (if new seizure without identified cause or known seizure history with new neurologic signs/symptoms)
- LP (if fever or meningismus)
- EEG

**Treatment**
- Avoid precipitating factors
- Indications for medical therapy (anticonvulsants): 2 or more unprovoked seizures, known organic brain disease, EEG with epileptiform activity, first episode of status epilepticus, abnormal neurologic examination or findings on neuroimaging
- Psychosocial issues: stigma of seizures, education of patient and family, status of driver’s license, pregnancy issues
- Safety issues: driving, operating heavy machinery, bathing, swimming alone
- Consider surgical treatment if focal and refractory

**Status Epilepticus**

- **Definition:** unremitting seizure or successive seizures without return to a baseline state of greater than 5 min
- **Complications:** anoxia, cerebral ischemia and cerebral edema, MI, arrhythmias, cardiac arrest, rhabdomyolysis and renal failure, aspiration pneumonia/pneumonitis, death (20%)
• initial measures: ABCs, vitals, monitors, capillary glucose (STAT), ECG, nasal O₂, IV NS, IV glucose, IV thiamine, ABGs (if respiratory distress/cyanotic)
• blood work: electrolytes, Ca²⁺, Mg²⁺, PO₄³⁻, glucose, CBC, toxicology screen, EtOH level, AED levels
• focused history: onset, past history of seizures, drug and alcohol ingestion, past medical history, associated symptoms, witnesses/collateral history
• physical exam (once seizures controlled): LOC, vitals, HEENT (nuchal rigidity, head trauma, tongue biting, papilledema), complete neurological exam, signs of neurocutaneous disorders, decreased breath sounds, cardiac murmurs or arrhythmias, urinary incontinence, MSK exam (rule out injuries)
• post-treatment stabilization: CT head, EEG, Foley catheter to monitor urine output, urine toxicology screen, monitor for rhabdomyolysis, and IV fluids to maintain normal cerebral perfusion pressure

Figure 17. Status epilepticus treatment algorithm

Antiepileptic Drugs
• generalized-onset and partial-onset seizures: lamotrigine (Lamictal*), levetiracetam (Keppra*), rufinamide (Banzel*), topiramate (Topamax*), valproic acid (Depakene*, Apo-Valproic*), divalproex sodium (Epival*), zonisamide
• partial seizures (simple partial, complex partial, and secondarily generalized seizures): carbamazepine (Tegretol*), gabapentin (Neurontin*), lacosamide (Vimpat*), oxcarbazepine (Trileptal*), phenobarbital (Phenobarb*), phenytoin (Dilantin*), pregabalin (Lyrica*), primidone, tiagabine (Gabitril*), vigabatrin (Sabril*) note: these drugs may exacerbate generalized seizures
• absence seizures: ethosuximide (Zarontin*)
**Behavioural Neurology**

- see Psychiatry, PS20

### Acute Confusional State/Delirium

**Table 12. Selected Intracranial Causes of Acute Confusion**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Thunderclap H/A</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Meningism</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td>CT with contrast (often ring enhancing lesion)</td>
</tr>
<tr>
<td>Infections</td>
<td>Fever, H/A, nausea, photophobia Meningismus</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Fever, H/A, ± seizure</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Increased ICP</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td>CT, LP</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Trauma Hx</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td>MRI</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Skin rash, active joints</td>
<td>ANA, ANCA, RF MRI, Angiography</td>
</tr>
<tr>
<td></td>
<td>Onset: Psychiatric features, memory loss, seizures Delayed: Movement disorder, and changes in blood pressure, heart rate, and temperature</td>
<td>CSF (test for presence of antibodies)</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Increased ICP</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td></td>
<td>Focal neurological signs</td>
<td>MRI</td>
</tr>
<tr>
<td>Seizure</td>
<td>Status epileptic</td>
<td>EEG</td>
</tr>
<tr>
<td>Primary</td>
<td>Psychotic disorder, mood disorder, anxiety disorder</td>
<td>No specific tests</td>
</tr>
<tr>
<td>Primary</td>
<td>Psychotic disorder, mood disorder, anxiety disorder</td>
<td>No specific tests</td>
</tr>
<tr>
<td>Other</td>
<td>Chest pain, cough with black sputum, new-onset seizure, HTN, increased ICP, dyspnea</td>
<td>Vital signs Serum chemistry and electrolyte analysis</td>
</tr>
<tr>
<td>Other</td>
<td>Brushing, dry skin and mucous membranes, mydriasis with loss of accommodation</td>
<td>Serum chemistry and electrolyte analysis</td>
</tr>
</tbody>
</table>

**Mild Neurocognitive Disorder (Mild Cognitive Impairment)**

**Definition**
- cognitive impairment not meeting criteria of Major Neurocognitive Disorder
- several criteria proposed with considerable overlap
- in general, criteria include a measurable cognitive deficit in at least one domain reported by patient or others without impairment in ADLs and in the absence of Major Neurocognitive Disorder
- amnestic (precursor to AD) vs. Non-amnestic MCI

**Pathophysiology**
- genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
    - the E4 polymorphism of apolipoprotein E (ApoE) is a susceptibility genotype (E2 is protective)
    - note: ApoE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
- pathology (not necessarily specific for AD)
  - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
    - senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
    - loss of synapses
    - neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
    - loss of cholinergic neurons in nucleus basalis of Meynert which normally project diffusely throughout the cortex

**Delirium**
- a medical emergency carrying significant risk of morbidity and mortality; it is characterized by acute onset, disorientation, fluctuating level of consciousness, poor attention, and marked psychomotor changes

**Visual hallucinations**
- more commonly indicate organic disease
biochemical pathology
- 50-90% reduction in action of choline acetyltransferase

Epidemiology
- published prevalence rates vary from 2-4 percent to more than 20 percent due to different diagnostic criteria and measuring instruments

Risk Factors
- elevated blood pressure, obesity, cardiac disease, and apolipoprotein E epsilon 4 genotype associated with increased risk of mild NCD

Signs and Symptoms
- cognitive impairment
  - particularly in amnestic subtype
  - important to ascertain that memory complaints represent change from baseline
  - patients with mild NCD are often troubled by memory symptoms in comparison to patients with dementia
- neuropsychiatric symptoms
  - depression (50%), irritability, anxiety, aggression, and apathy

Investigations
- establish a baseline for follow-up
- office evaluation
  - clinical interview is the cornerstone of mild NCD evaluation
  - ideally informants should be involved in the interview
  - consider drop-off in personal care and ADLs at later stage
- neuropsychological testing
  - MMSE or MoCA
  - should not be used in isolation
  - if abnormal, follow-up in one year to monitor for cognitive and functional decline
- neuroimaging
  - role uncertain
  - most advocate for a non-contrast brain CT to evaluate for structural abnormalities (CVD, SDH, NPH, or mass lesion)
- other testing
  - exclude treatable conditions and underlying psychiatric conditions

Treatment
- watch and wait
- no evidence for cholinesterase inhibitors, anti-inflammatory agents, vascular risk factor modification, exercise, cognitive interventions

Prognosis
- 10% progress to dementia per yr
- typically progress to dementia over a period of 2-3 yr

Major Neurocognitive Disorder (formerly Dementia)
- see Psychiatry, PS21 and Geriatric Medicine, GM4

Definition
- an acquired, generalized, and (usually) progressive impairment of cognitive function (i.e. memory, recall, orientation, language, abstraction) associated with impairment in activities of daily living (i.e. planning, shopping, food preparation, difficulties with finances)
- affects comprehension, but not level of consciousness
- diagnosis of major NCD requires presence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on:
  A) concern of the individual or a knowledgeable informant AND
  B) a substantial impairment in cognitive performance either documented by standardized neuropsychological testing, or quantified clinical assessment
- see Psychiatry, PS21 for DSM-5 diagnostic criteria
- differentiated from mild NCD (formerly mild cognitive impairment) by the extent to which the impairment affects ADLs
  - mild NCD represents an intermediate stage between dementia and normal aging
  - by definition, IADLs are not affected in mild NCD

Epidemiology
- major NCD (dementia): 1-2% at age 65 yr and reaching as high as 30% by age 85 yr
- mild NCD: 2-10% at age 65 yr and 5-25% by age 85 yr
- **note** major NCD due to Alzheimer's disease is uncommon before age 60 yr
- major NCD due to frontotemporal lobar degeneration has an earlier onset and represents a progressively smaller fraction of all NCDs with age

**Etiology**
- see Table 13 for common causes of dementia
- see Table 14 for acquired causes of dementia
- reversible causes: alcohol (intoxication or withdrawal, Wernicke's encephalopathy), medication (benzodiazepines, anticholinergics), heavy metal toxicity, hepatic or renal failure, B12 deficiency, glucose, cortisol, thyroid dysfunction, NPH, depression (pseudodementia), intracranial tumour, SDH, hypercalcemia (secondary to elevated PTH)
- must rule out delirium

**History**
- "geriatric giants"
  - confusion/incontinence/falls/polypharmacy
  - memory and safety (wandering, leaving doors unlocked, leaving stove on, losing objects)
  - behavioural (mood, anxiety, psychosis, suicidal ideation, personality changes, aggression)
- ADLs and IADLs
- cardiovascular, endocrine, neoplastic, renal ROS
- alcohol, smoking
- OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
- history of vascular disease or head trauma
- collateral history

**Investigations**
- depends on suspected etiologies (see Tables 13 and 14)
  - blood pressure
  - hearing and vision
  - neurological exam with attention to signs of parkinsonism, UMN findings, CVD
  - general physical exam depending on risk factors and history
  - MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)
  - blood pressure
  - neurological exam with attention to signs of parkinsonism, UMN findings, CVD
  - OTCs, herbal remedies, medications (sedative hypnotics, antipsychotics, antidepressants, anticholinergics), compliance, accessibility
  - history of vascular disease or head trauma
  - collagen history

**Physical Exam**
- blood pressure
- hearing and vision
- neurological exam with attention to signs of parkinsonism, UMN findings, CVD
- general physical exam depending on risk factors and history
- MMSE or MoCA, clock drawing, frontal lobe testing (go/no-go, word lists, similarities, proverb)

<table>
<thead>
<tr>
<th>PRIMARY DEGENERATIVE</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Memory impairment</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Aphasia, apraxia, agnosia</td>
<td></td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Fluctuating cognition</td>
<td></td>
</tr>
<tr>
<td>Frontotemporal dementia (e.g. Pick’s disease)</td>
<td>Behavioural presentation: Disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Language presentation: Progressive non-fluent aphasia, semantic dementia</td>
<td></td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Chorea</td>
<td>Genetic testing</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>VASCULAR</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular cognitive impairment (previously Multi-infarct dementia)</td>
<td>Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait)</td>
<td>CT or MRI, SPECT</td>
</tr>
<tr>
<td></td>
<td>Dysexecutive syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>May be abrupt onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stepwise deterioration is classic but progressive deterioration is most common</td>
<td></td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>Systemic S&amp;S of vasculitis</td>
<td>ANA; ANCA; RF CT or MRI Angiography</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Sensitivity and Specificity</th>
<th>Tool</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>87%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>85%</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>Judgment</td>
<td>76%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>DSM IV</td>
<td>76%</td>
<td>80%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Vitamin B12 Deficiency Symptoms</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Macrocyclic anemia, pallor, SOB, fatigue, chest pain, palpitations</td>
<td></td>
</tr>
<tr>
<td>Confusion or change in mental status (if advanced)</td>
<td></td>
</tr>
<tr>
<td>Decreased vibration sense</td>
<td></td>
</tr>
<tr>
<td>Distal numbness and paresthesia</td>
<td></td>
</tr>
<tr>
<td>Weakness with UMN findings</td>
<td></td>
</tr>
<tr>
<td>Diarrhea, anorexia</td>
<td></td>
</tr>
</tbody>
</table>

**Dementia DDx**
- Alzheimer’s disease
- Vascular dementia (multi-infarct dementia)
- Huntington’s disease, CJD
- Infection (postencephalitis, HIV)
- NPH
- Metabolic (DM)
- Intraocular tumour
- Trauma (head injury)
- Anoxia
- Endocrine (hypothyroid)
- Space occupying lesion (chronic SDH)
- Toxic (alcohol)

**Cholinesterase Inhibitors for Dementia with Lewy Bodies (DLB), Parkinson’s Disease (PDD) and Cognitive Impairment in Parkinson’s Disease (CIND-PD)**
- **Cochrane DB Syst Rev 2012;3:CD006504**
- **Study:** Meta-analysis of RCTs assessing efficacy of treatment with cholinesterase inhibitors in DLB, PDD, and CIND-PD.
- **Results:** The six trials (n = 1,236) included demonstrated therapeutic benefit of cholinesterase inhibitors for global assessment, cognitive function, behavioural disturbance, and activities of daily living. Cholinesterase inhibitors were associated with increased adverse events (OR 1.64) and drop out (OR 1.94). Adverse events were more common with rivastigmine than donepezil, husted or bold. Withdrawal occurred in the treatment group (OR 0.29).
- **Conclusion:** Current evidence supports use of cholinesterase inhibitors for patients with PDD but its role in DLB and CIND-PD is still unclear.

<table>
<thead>
<tr>
<th>Table 13. Common Causes of Major NCD (Dementia)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td><strong>Key Clinical Features</strong></td>
</tr>
<tr>
<td>Alzheimer’s disease</td>
<td>Memory impairment, aphasia, apraxia, agnosia</td>
</tr>
<tr>
<td>Dementia with Lewy bodies</td>
<td>Visual hallucinations, parkinsonism</td>
</tr>
<tr>
<td>Frontotemporal dementia (e.g. Pick’s disease)</td>
<td>Behavioural presentation, disinhibition, perseveration, decreased social awareness, mental rigidity, memory relatively spared</td>
</tr>
<tr>
<td>Huntington’s disease</td>
<td>Chorea</td>
</tr>
<tr>
<td>Vascular cognitive impairment (previously Multi-infarct dementia)</td>
<td>Bradyphrenia without features of parkinsonism (slow thinking, slow rate of learning, slow gait)</td>
</tr>
<tr>
<td>CNS vasculitis</td>
<td>Systemic S&amp;S of vasculitis</td>
</tr>
</tbody>
</table>

Dementia Considerations for Management
- ABCDs
- Affective disorders, ADLs
- Behavioural problems
- Caretaker, Cognitive medications and stimulation
- Directives, Driving
- Sensory enhancement (glasses/hearing aids)
Table 14. Acquired Causes of Major NCD (Dementia)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>INFECTIOUS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic meningitis</td>
<td>Fever, H/A, nausea, Meningismus</td>
<td>CT, LP</td>
</tr>
<tr>
<td></td>
<td>Localizing neurological deficits</td>
<td></td>
</tr>
<tr>
<td>Chronic encephalitis</td>
<td>Fever, headache</td>
<td>CT or MRI</td>
</tr>
<tr>
<td>Chronic abscess</td>
<td>Increased ICP, Localizing neurological deficits</td>
<td>CT with contrast</td>
</tr>
<tr>
<td>HIV</td>
<td>See Infectious Diseases, ID28</td>
<td>HIV serology</td>
</tr>
<tr>
<td>Creutzfeldt-Jakob disease</td>
<td>Rapidly progressive, myoclonus</td>
<td>EEG, CT or MRI, LP</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Ataxia, myoclonus, tabes dorsalis</td>
<td>LP, CT, or MRI, VDRL</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRAUMATIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diffuse axonal shear, epidural hematoma, subdural hematoma, SDH</td>
<td>Trauma Hx, Increased ICP, papilledema, Localizing neurological signs</td>
<td>CT (non-contrast)</td>
</tr>
<tr>
<td>RHEUMATOLOGIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>See Rheumatology, RH11</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>ANA, anti-dsDNA</td>
<td></td>
</tr>
<tr>
<td>NEOPLASTIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mass effect/edema, hemorrhage, seizure</td>
<td>Increased ICP, Localizing neurological signs</td>
<td>CT with contrast</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MRI</td>
</tr>
</tbody>
</table>

**Major or Mild NCD due to Alzheimer’s Disease**

- see Psychiatry, PS22

**Definition**
- beyond criterion for NCD, the core features of major or mild NCD due to Alzheimer’s disease include an insidious onset and gradual progression of cognitive and behavioural symptoms
- typical presentation: amnestic (i.e. impairment in memory and learning - impaired ability to learn new information)
  - mild phase: impairment in memory and learning sometimes accompanied with deficits in executive function
  - moderate-severe phase: visuocognitive/perceptual-motor ability and language may also be impaired
  - social cognition tends to be preserved until late in the course of the disease
- atypical nonamnestic presentation (one of the following)
  1. aphasia: language disturbance
  2. apraxia: impaired ability to carry out motor activities despite intact motor function
  3. agnosia: failure to recognize or identify objects despite intact sensory function
- note: there may be no evidence of mixed etiology (i.e. absence of other neurodegenerative or CVD)

**Pathophysiology**
- genetic factors
  - minority (<7%) of AD cases are familial (autosomal dominant)
  - 3 major genes for autosomal dominant AD have been identified:
    - amyloid precursor protein (chromosome 21), presenilin 1 (chromosome 14), presenilin 2 (chromosome 1)
    - the E4 polymorphism of apolipoprotein E (APOE) is a susceptibility genotype (E2 is protective)
  - note: APOE cannot serve as a diagnostic marker because it is only a risk factor and neither necessary nor sufficient for disease occurrence
- pathology (although not necessarily specific for AD)
  - gross pathology
    - diffuse cortical atrophy, especially frontal, parietal, and temporal lobes (hippocampi)
  - microscopic pathology
    - senile plaques (extracellular deposits of amyloid in the grey matter of the brain)
    - loss of synapses
    - neurofibrillary tangles (intracytoplasmic paired helical filaments with amyloid and hyperphosphorylated Tau protein)
    - loss of cholinergic neurons in nucleus basalis of Meynert that project diffusely throughout the cortex
  - biochemical pathology
    - 50-90% reduction in action of choline acetyltransferase

**Early Signs of Dementia/Major NCD**

<table>
<thead>
<tr>
<th>Normal Aging</th>
<th>Normal Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forgetting the names of close relations</td>
<td>Forgetting the names of acquaintances</td>
</tr>
<tr>
<td>Increased frequency of forgetting</td>
<td>Briefly forgetting part of an experience</td>
</tr>
<tr>
<td>Repeating phrases/stories in the same conversation</td>
<td>Not putting away things properly</td>
</tr>
<tr>
<td>Unpredictable mood changes</td>
<td>Mood changes in response to appropriate causes</td>
</tr>
<tr>
<td>Decreased interest in activities and difficulty making choices</td>
<td>Changes in usual interests</td>
</tr>
</tbody>
</table>

**4 As and one D of AD**

- Anterograde amnesia
- Aphasia
- Apraxia
- Agnosia
- Disturbance in executive function

(Anterograde amnesia plus at least one of the other features is required for AD diagnosis)

Down syndrome predisposes to early onset of Alzheimer’s (i.e. age of ~40) due to three copies of the amyloid gene (APP)
Epidemiology
• 1/12 of population 65-75 yr of age
• up to 1/3 population >85 yr of age
• accounts for 60-90% of all dementias (depending on setting and diagnostic criteria)

Risk Factors
• age is the largest risk factor
• genetic susceptibility polymorphism: apolipoprotein E4 increases risk and decreases age of onset
• other factors include: traumatic brain injury, family history, Down syndrome, low education, and presence of multiple vascular risk factors (e.g. smoking, HTN, hypercholesterolemia, DM)

Signs and Symptoms
• cognitive impairment
  ▫ memory impairment for newly acquired information (early)
  ▫ deficits in language, abstract reasoning, and executive function
• behavioural and psychiatric manifestations (80% of those with major NCD)
  ▫ mild NCD: major depressive disorder and/or apathy
  ▫ major NCD: psychosis, irritability, agitation, combative, and wandering
• motor manifestations (late)
  ▫ gait disturbance, dysphagia, incontinence, myoclonus, and seizures
  ▫ parkinsonism (if present consider DLB)

Investigations
• perform investigations to rule out other potentially reversible causes of dementia
• EEG: usually normal, may observe generalized slowing (nonspecific)
• MRI: preferential atrophy of the hippocampi and precuneus of the parietal lobe; dilatation of lateral ventricles; widening of cortical sulci
• SPECT: hypoperfusion in temporal and parietal lobes
• PET imaging using Pittsburgh compound B (PIB) as a tracer enables imaging of beta-amyloid plaque in neuronal tissue

Treatment
• acetylcholinesterase inhibitors have been shown to slow decline in cognitive function
  ▫ donepezil, rivastigmine, galantamine
• relative contraindications: bradycardia, heart block, arrhythmia, CHF, CAD, asthma, COPD, ulcers, or risk factors for ulcers and/or GI bleeding
• galantamine is contraindicated in patients with hepatic/renal impairment
• memantine is an NMDA-receptor antagonist that has some benefits in later stage AD (i.e. when MMSE <17)
• symptomatic management
  1. pharmacologic
     ▫ low dose neuroleptics for agitation (neuroleptics may worsen cognitive decline)
     ▫ trazodone for sleep disturbance
     ▫ antidepressants (SSRIs)
  2. non-pharmacologic
     ▫ redirection
     ▫ explore inciting factors for behaviour and modify behaviour of patient or caregiver
     ▫ family support and day care facilities

Prognosis
• mean duration of survival after diagnosis is approximately 10 yr, reflecting the advanced age of the majority of individuals rather than the course of the disease
• in those who survive the full course, death commonly results from aspiration

Major or Mild NCD with Lewy Bodies
(formerly Dementia with Lewy Bodies)

Definition
• A NCD that includes not only progressive cognitive impairment (with early changes in complex attention and executive function rather than learning and memory), but also recurrent complex visual hallucinations
• core diagnostic features
  ▫ fluctuating cognition with pronounced variations in attention and alertness
  ▫ recurrent visual hallucinations that are well formed and detailed
  ▫ spontaneous features of parkinsonism, with onset subsequent to development of cognitive decline (rest tremor may be absent in DLB, but otherwise same classic features of Parkinson’s disease)
• suggestive/supportive features
  ▫ meets criteria for rapid eye movement (REM) sleep behaviour disorder
  ▫ severe sensitivity to neuroleptic medications (rigidity, neuroleptic malignant syndrome, extrapyramidal symptoms)

Cognitive Effects of Atypical Antipsychotic Medications in Patients with Alzheimer’s Disease: Outcomes from CATIE-AD
Am J Psychiatry 2011;168:831-839
Study: 421 outpatients with Alzheimer’s disease and psychosis or agitated/aggressive behaviour were randomized to receive olanzapine, quetiapine, risperidone, or placebo in a multicentre double-blinded RCT. MMSE and Alzheimer’s Disease Assessment Scale (ADAS) scores were measured at 36 wk.
Results: Patients receiving atypical antipsychotics exhibited a faster rate of cognitive decline as measured by MMSE scores (- 0.067/wk vs. -0.007/wk). They also had a significantly faster decline compared to placebo on a composite measure of ADAS, MMSE, and various other cognitive tests (-0.011/wk vs. -0.001/wk).
Conclusions: Long-term use of atypical antipsychotics for behavioural symptoms and psychosis in dementia patients is associated with greater rates of cognitive decline.
repeated falls, syncope, or transient episodes of unexplained loss of consciousness
- auditory or other nonvisual hallucinations, systematic delusions, and depression may also be present

**Etiology and Pathogenesis**
- Lewy bodies (eosinophilic cytoplasmic inclusions) found in both cortical and subcortical structures
- mixed DLB and AD pathology is common

**Diagnostically Suggestive Markers**
- low striatal dopamine transporter uptake on SPECT or PET
- relative preservation of medial temporal structures on CT/MRI

**Epidemiology**
- 0.1-5% of the general elderly population
- Lewy bodies are present in 20-35% of all dementia cases (more common in males)

**Treatment**
- acetylcholinesterase inhibitors (e.g. donepezil)

**Prognosis**
- average duration of survival 5-7 yr

---

**Major or Mild Frontotemporal NCD**
*(formerly Frontotemporal Dementia)*

**Definition**
- refers to a group of disorders caused by progressive cell degeneration in the brain's frontal or temporal lobes
- there are several variants of FTD each with specific core symptoms
- nevertheless, there is overlap between variants (i.e. NCD criteria along with relative sparing of learning and memory and perceptual-motor function)
- common neurocognitive symptoms include deficits in executive function (e.g. poor mental flexibility, abstract reasoning, response inhibition, planning/organization, and increased distractibility)
- “probable” is distinguished from “possible” frontotemporal NCD by:
  - evidence of causative frontotemporal NCD genetic mutation, from either family history or genetic testing
  - evidence of disproportionate frontal and/or anterior temporal atrophy on MRI or CT
  - evidence of frontal and/or anterior temporal hypoperfusion or hypometabolism on PET or SPECT

**Behavioural Variant FTD**
- most common variant; disinhibition and apathy are common symptoms
- insidious onset: must show progressive deterioration of behaviour and/or cognition by observation or history
- prominent decline in social cognition and/or executive abilities
- typically early symptom presentation (i.e. within the first 3 yr)
- three out of the following symptoms must be present and persistent/recurrent:
  - behavioural disinhibition (socially inappropriate behaviour, impulsive, careless)
  - apathy or inertia
  - loss of sympathy or empathy (diminished response to others’ needs/feelings, social interest)
  - preservative, stereotyped, or compulsive/ritualistic behaviour
  - hyperorality and dietary changes (binge eating, increased consumption of alcohol/cigarettes or inedible objects)

**Language Variants (Primary Progressive Aphasia)**
- prominent decline in language ability, in the form of speech production, word finding, object naming, grammar, or word comprehension
- three subtypes
  - nonfluent/agrammatic variant PPA (NFAV-PPA) or progressive nonfluent aphasia (PNFA): non-fluent, laboured articulation/speech, anomia, preserved single word comprehension, word-finding deficit, impaired repetition
  - semantic variant PPA (SV-PPA) or semantic dementia (SD): fluent, normal rate, anomia, impaired single word comprehension, intact repetition, use words of generalization (“thing”) or supraordinate categories (“animal” for “dog”)
  - logopenic progressive aphasia (LPA): naming difficulty and impaired repetition
FTD Movement Disorders
- corticobasal degeneration (CBD): shakiness, lack of coordination, muscle rigidity and spasms
- progressive supranuclear palsy (PSP): walking and balance problems; frequent falls and muscle stiffness

Etiology and Pathogenesis
- unknown, however there is likely a genetic/familial component (40% have family history of early onset NCD)
- genetic variants: MAPT gene (Tau), PGRN gene (progranulin), VCP gene, TARDBP gene (TDP-43), CHMP2D gene
- unlike AD, FTD does not show amyloid plaques or neurofibrillary tangles, instead it is characterized by severe atrophy and specific neuronal inclusion bodies
- gross changes: atrophy in the frontal and anterior temporal lobes; cortical thinning; possible ventricular enlargement
- histological changes: gliosis, swollen neurons, microvacuolation, inclusion bodies in neurons/glia (Tau or TDP-43)

Epidemiology
- fourth most common cause of dementia (5% of all dementia cases)
- common cause of early-onset NCD in individuals younger than 65 yr

Prognosis
- median survival being 6-11 yr after symptoms onset and 3-4 yr after diagnosis
- survival is shorter and decline is faster than in typical Alzheimer's disease

Major or Mild Vascular NCD

Definition
- diagnosis of major or mild NCD with determination of CVD as the dominant if not exclusive pathology that accounts for the cognitive deficits
- vascular etiology suggested by one of the following:
  - onset of cognitive deficits is temporally related to one or more cerebrovascular events
  - evidence for decline is prominent in complex attention (including processing speed) and frontal-executive function
  - evidence of the presence of CVD from history, physical exam, and/or neuroimaging that is sufficient to account for the neurocognitive deficits
  - neuroimaging evidence of cerebrovascular disease comprises one or more of the following:
    - one or more large vessel infarct or hemorrhage
    - a strategically placed single infarct or hemorrhage (e.g. angular gyrus, thalamus, basal forebrain)
    - two or more lacunar infarcts outside the brainstem
    - extensive and confluent white matter lesions
    - for mild vascular NCD: history of a single stroke or extensive white matter disease is sufficient
    - for major vascular NCD: history of two or more strokes, a strategically placed stroke, or a combination of white matter disease and one or more lacunae is generally necessary
    - associated features supporting diagnosis: personality and mood changes, abulia, depression, emotional lability, and psychomotor slowing

Etiology and Pathogenesis
- major risk factors are the same as those for CVD (i.e. HTN, DM, smoking, obesity, high cholesterol levels, high homocysteine levels, other risk factors for atherosclerosis, atrial fibrillation, and conditions increasing risk of cerebral emboli)
- major or mild vascular NCD with gradual onset and slow progression is generally due to small vessel disease leading to lesions in white matter, basal ganglia, and/or thalamus
- cognitive deficits can be attributed to disruption of cortical-subcortical circuits

Epidemiology
- second most common cause of NCD
- prevalence estimates for vascular dementia/NCD range from 0.2-13% (by age 70), 16% (ages 80+) to 44.6% (ages 90+)
- higher prevalence in African Americans compared to Caucasians and East Asians
- prevalence higher in males than in females

Creutzfeldt-Jakob Disease
- rare degenerative fatal brain disorder caused by prion proteins causing spongiform changes, astrocytosis, and neuronal loss
- most common forms are sporadic (85%), hereditary (5-10%), and acquired (<1%)
- investigations: CSF analysis, MRI brain (cortical and/or subcortical FLAIR changes), EEG (periodic complexes)
- definitive diagnosis is by brain biopsy
- no treatments currently exist
Normal Pressure Hydrocephalus

- see Neurosurgery, NS8

Aphasia

Definition
- an acquired disturbance of language characterized by errors in speech production, writing, comprehension, or reading

Neuroanatomy of Aphasia
- Broca’s area (posterior inferior frontal lobe) involved in speech production (expressive)
- Wernicke’s area (posterior superior temporal lobe) involved in comprehension of language (receptive)
- angular gyrus is responsible for relaying written visual stimuli to Wernicke’s area for reading comprehension
- arcuate fasciculus association bundle connects Wernicke’s and Broca’s areas

Assessment of Language
- assessment of context
  - handedness (writing, drawing, toothbrush, scissors), education level, native language, learning difficulties
- assessment of aphasia
  - spontaneous speech (fluency, paraphasias, repetition, naming, comprehension – auditory and reading, writing, neologisms)

Apaxia classification

Figure 19. Aphasia classification

Apraxia

Definition
- inability to perform skilled voluntary motor sequences that cannot be accounted for by weakness, ataxia, sensory loss, impaired comprehension, or inattention
Clinicalpathological Correlations

Table 15. Apraxia

<table>
<thead>
<tr>
<th>Description</th>
<th>Tests</th>
<th>Hemispheres</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ideomotor</td>
<td>Inability to perform skilled learned motor sequences</td>
<td>Left</td>
</tr>
<tr>
<td>Ideational</td>
<td>Inability to sequence actions</td>
<td>Right and left</td>
</tr>
<tr>
<td>Constructional*</td>
<td>Inability to draw or construct</td>
<td>Right and left</td>
</tr>
<tr>
<td>Dressing*</td>
<td>Inability to dress</td>
<td>Right</td>
</tr>
</tbody>
</table>

*Refers specifically to the inability to carry out the learned movements involved in construction, drawing, or dressing; not merely the inability to construct, draw, or dress. Many skills aside from praxis are needed to carry out these tasks.

Agnosia

Definition

• disorder in the recognition of the significance of sensory stimuli in the presence of intact sensation and naming

Clinicalpathological Correlations

Table 16. Agnosias

<table>
<thead>
<tr>
<th>Description</th>
<th>Lesion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apperceptive Visual Agnosia</td>
<td>Inability to name or demonstrate the use of an object presented visually to distorted visual perception</td>
</tr>
<tr>
<td></td>
<td>Recognition by touch remains intact</td>
</tr>
<tr>
<td>Associative Visual Agnosia</td>
<td>Inability to name an object presented visually to disconnect between visual cortex and language areas</td>
</tr>
<tr>
<td></td>
<td>Visual perception is intact as demonstrated by visual matching</td>
</tr>
<tr>
<td>Prosopagnosia</td>
<td>Inability to recognize familiar faces in the presence of intact visual perception and intact auditory recognition</td>
</tr>
<tr>
<td>Colour Agnosia</td>
<td>Inability to perceive colour</td>
</tr>
<tr>
<td>Impaired Stereognosia</td>
<td>Inability to identify objects by touch</td>
</tr>
<tr>
<td>Finger Agnosia</td>
<td>Inability to recognize, name, and point to individual fingers</td>
</tr>
</tbody>
</table>

Mild Traumatic Brain Injury

Definition

• mild TBI = concussion
• trauma induced transient alteration in mental status that may involve loss of consciousness
• hallmarks of concussion: confusion and amnesia, which may occur within minutes
• loss of consciousness (if present) must be less than 30 min, initial GCS must be between 13-15, and post-traumatic amnesia must be less than 24 h

Epidemiology

• 75% of TBIs are estimated to be mild; remainder are moderate or severe (see Neurosurgery, NS31 and Emergency Medicine, ER9)
• highest rates in children 0-4 yr, adolescents 15-19 yr, and elderly >65 yr

Clinical Features

• impairments following mild TBI
  • somatic: headache, sleep disturbance, nausea, vomiting, blurred vision
  • cognitive dysfunction: attentional impairment, reduced processing speed, drowsiness, amnesia
  • emotion and behaviour: impulsivity, irritability, depression
  • severe concussion: may precipitate seizure, bradycardia, hypotension, sluggish pupils
  • associated conditions: brain contusion, diffuse axonal injury, C-spine injury

Investigations

• neurological exam to identify focal neurologic deficits
• neurocognitive assessment
  • simple orientation questions are inadequate to detect cognitive changes
  • initial assessment of severity is determined by
    • Glasgow Coma Scale: mild: 13-15, moderate: 9-12, severe: 3-8
    • sideline evaluation: Standardized Assessment of Concussion, Westmead Post-Traumatic Amnesia Scale, Sport Concussion Assessment Tool
• neuroimaging
  ▪ x-ray of skull: not indicated for routine evaluation of MTBI
  ▪ CT head as indicated by Canadian CT Head Rules (see Emergency Medicine, ER8)
  ▪ MRI not indicated in initial evaluation – indicated in presence of continued or worsening symptoms despite normal CT

Treatment
• observation for first 24 h after mild TBI in all patients because of risk of intracranial complications
• emergency department for assessment if any loss of consciousness or persistent symptoms
• hospitalization with normal CT if GCS <15, seizures, or bleeding diathesis; or abnormal CT scan
• early rehabilitation to maximize outcomes
  ▪ OT, PT, SLP, vestibular therapy, driving, therapeutic recreation
• pharmacological management of headaches, pain, depression
  ▪ CBT, relaxation therapy
• follow Return to Play guidelines (www.thinkfirst.ca)

Prognosis
• most recover from mild TBI with minimal treatment, but some experience long-term consequences
• athletes with a previous concussion are at increased risk of subsequent concussion and cumulative brain injury
• repeat TBI can lead to life threatening cerebral edema (controversially known as second impact syndrome) or permanent impairment
• sequelae include
  ▪ post-concussion syndrome: dizziness, headache, neuropsychiatric symptoms, cognitive impairment (usually resolves within weeks to months)
  ▪ post-traumatic headaches: begin within 7 d of injury
  ▪ post-traumatic epilepsy: two-fold increase in risk of epilepsy in 5 yr post-TBI, prophylactic anticonvulsants not effective
  ▪ post-traumatic vertigo

Neuro-Oncology

Paraneoplastic Syndromes
• see Endocrinology, E51

Tumours of the Nervous System
• see Neurosurgery, NS10

Movement Disorders

Overview of Movement Disorders

<table>
<thead>
<tr>
<th>Table 17. Movement Disorder Definitions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akathisia</td>
</tr>
<tr>
<td>Asterix</td>
</tr>
<tr>
<td>Athetosis</td>
</tr>
<tr>
<td>Bradykinesia</td>
</tr>
<tr>
<td>Chorea</td>
</tr>
<tr>
<td>Dyskinesia</td>
</tr>
<tr>
<td>Dystonia</td>
</tr>
<tr>
<td>Freezing</td>
</tr>
<tr>
<td>Hemiballismus</td>
</tr>
<tr>
<td>Myoclonus</td>
</tr>
<tr>
<td>Myokymia</td>
</tr>
<tr>
<td>Tachykinsia</td>
</tr>
<tr>
<td>Tics</td>
</tr>
<tr>
<td>Tremor</td>
</tr>
</tbody>
</table>

In some cases, dystonias may only occur during voluntary movement and sometimes only during specific activities such as writing, chewing, or speaking.

Hemiballismus is most often due to a vascular lesion of the contralateral subthalamic nucleus.

Some myoclonus is stimulus sensitive and can be induced by noise, movement, light, visual threat, or pinprick.
Function of the Basal Ganglia

- The cerebral cortex initiates movement via excitatory (glutamatergic) projections to the striatum, which then activate two pathways: direct and indirect.
  - Direct: cortex → striatum → GPi/SNr → thalamus → motor cortex
    * Activation of this pathway removes the inhibitory effect of the GPi on the thalamus, letting the thalamus activate the cortex and ultimately allowing movement.
  - Indirect: cortex → striatum → GPe → STN → GPi/SNr → thalamus → motor cortex
    * Activation of this pathway causes inhibition of the thalamus and ultimately prevents movement.

![Neural connections of the basal ganglia](image1)

**Figure 20. Neural connections of the basal ganglia**

![Horizontal section of basal ganglia](image2)

**Figure 21. Horizontal section of basal ganglia**
**Movement Disorders**

Differential Diagnoses
1. Tremor
   - **postural:** physiologic, anxiety, sedative/alcohol withdrawal, drug toxicity, heavy metal poisoning, carbon monoxide poisoning, thyrotoxicosis, benign essential tremor, cerebellar, Wilson's disease
     - benign essential tremor is a common autosomal dominant trait that presents as a bilateral postural tremor of the vertical axis, especially in the upper extremities
   - **intention:** brainstem lesion, cerebellar lesion, alcohol, anticonvulsants, sedatives, Wilson's disease
   - **resting:** Parkinsonism, Wilson's disease, mercury poisoning

### Table 18. Approach to Tremors

<table>
<thead>
<tr>
<th>Body Part</th>
<th>Resting</th>
<th>Postural</th>
<th>Intention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td>3-7 Hz pill rolling</td>
<td>6-12 Hz fine tremor</td>
<td>&lt;5 Hz coarse tremor</td>
</tr>
<tr>
<td>Worse with</td>
<td>Rest while concentrating “TRAP”</td>
<td>Sustained posture (outstretched arms)</td>
<td>Finger to nose</td>
</tr>
<tr>
<td>Associated Sx</td>
<td></td>
<td>≥ Autosomal dominant FHx</td>
<td>Cerebellar findings</td>
</tr>
<tr>
<td>DDx</td>
<td>PD, Parkinsonism, Wilson’s disease</td>
<td>Physiologic, benign essential, drugs, hyperthyroid, hyperglycemic</td>
<td>Cerebellar disorders, Wilson’s disease, alcohol, MS</td>
</tr>
<tr>
<td>Treatment</td>
<td>Carbipoda-levodopa (Sinemet®), surgery, DBS</td>
<td>Propranolol, anticonvulsants, primidone</td>
<td>Treat underlying cause</td>
</tr>
</tbody>
</table>

2. Chorea: Huntington’s disease, neuroacanthocytosis, SLE, APLA syndrome, Wilson’s disease, CVD, tardive dyskinesia, senile chorea, Sydenham’s chorea, pregnancy chorea

3. Dystonia
   - **primary dystonia:** familial, sporadic (torticollis, blepharospasm, writer’s cramp)
   - **dystonia-plus syndromes:** dopa-responsive dystonia, myoclonus-dystonia
   - **secondary dystonia:** thalatomy, stroke, CNS tumour, demyelination, PNS injury, drugs/toxins (L-dopa, neuroleptics, anticonvulsants, Mn, CO, cyanide, methanol)
   - **heredodegenerative dystonias:** Parkinsonian disorders, Wilson’s disease, Huntington’s disease

4. Myoclonus
   - **physiologic myoclonus:** hiccups, nocturnal myoclonus
   - **essential myoclonus
   - **epileptic myoclonus
   - **symptomatic myoclonus**
     - degenerative disorders (Wilson’s disease, Huntington’s disease, Corticobasal degeneration)
     - infectious disorders (CJD, viral encephalitis, AIDS-dementia complex)
     - metabolic disorders (drug intoxication/withdrawal, hypoglycemia, hyponatremia, HONK, hepatic encephalopathy, uremia, hypoxia)
     - focal brain damage (head injury, stroke, mass)

5. Tics
   - **primary tic disorders:** transient tic disorder, chronic tic disorder, Gilles de la Tourette, adult onset or senile
   - **secondary tic disorders:** encephalitis, CJD, Sydenham’s chorea, head trauma, drugs, mental retardation syndromes
   - association with OCD and ADHD

### Parkinson’s Disease

**Etiology**
- **sporadic:** combination of oxidative stress to dopaminergic neurons, environmental toxins (e.g. pesticides), accelerated aging, genetics
- **familial** (10%): autosomal dominant α-synuclein mutations, autosomal recessive parkin gene or DJ-1 gene mutation (juvenile onset)
- **MPTP** (neurotoxin)

**Epidemiology**
- prevalence of 0.3% in industrialized countries, but rises with increased age
- second most common neuro-degenerative disorder, after Alzheimer’s
- mean age of onset is 60 yr

In a young patient (<45) must do TSH (thyroid disease), ceruloplasmin (Wilson’s disease), and CT/MRI (cerebellar disease) as indicated by type of tremor

> 90% of essential tremor does not need treatment

Most common cause of chorea is drug therapy for PD

Palatal myoclonus can result from lesion to the Dentato-Rubro-Olivary tract, and is associated with an audible clicking

Key Parkinsonian Features
- **TRAP**
  - Tremor (resting)
  - Rigidity
  - Akinesia/bradykinesia
  - Postural instability

**Diagnostic Criteria**
- Bradykinesia, plus one of: resting tremor, muscle rigidity, postural instability not caused by other factors, OR
- 3 or more of the following features:
  - Resting tremor
  - Unilateral onset
  - Persistent asymmetry, with side of onset most affected
  - Progressive disorder
  - Excellent response (70-100%) to levodopa
  - Severe levodopa-induced chorea
  - Response to levodopa for 5 yr or more
  - Clinical course lasting 10 yr or more
Risk Factors
- family history, male, head injury, rural living, exposure to certain neurotoxins
- protective: coffee drinking, smoking, NSAID use, estrogen replacement in post-menopausal women

Pathophysiology
- loss of dopaminergic neurons in pars compacta of substantia nigra, thus reduced dopamine in striatum leading to disinhibition of the indirect pathway and decreased activation of the direct pathway causing increased inhibition of cortical motor areas
- α-synucleinopathy: α-synuclein accumulates in Lewy bodies and causes neurotoxicity in substantia nigra

Signs and Symptoms
- positive motor
  - resting tremor: asymmetric 4-5 Hz “pill-rolling” tremor, especially in hands
  - rigidity: lead-pipe rigidity with cogwheeling due to superimposed tremor
- negative motor
  - bradykinesia: slow, small amplitude movements, fatiguing of rapid alternating movements, difficulty initiating movement
- related findings: masked facies, hypophonia, aprosody (monotonous speech), dysarthria, micrographia, shuffling gait with decreased arm swing
- freezing: occurs with walking triggered by initiating stride or barriers/destinations, lasting seconds
- postural instability: late finding presenting as falls, festinating gait
- cognition: bradyphrenia (slow to think/respond), dementia (late finding)
- behavioural: decreased spontaneous speech, depression, sleep disturbances, anxiety
- autonomic: constipation, urinary retention, sexual dysfunction, later findings of orthostatic hypotension

Treatment
- pharmacologic
  - mainstay of treatment: levodopa/carbidopa (Sinemet®). Levodopa is a dopamine precursor; carbidopa decreases peripheral metabolism of levodopa, decreasing side effects and increasing half-life of levodopa
  - levodopa-related fluctuation: delayed onset of response (affected by mealtime), end-of-dose deterioration (“wearing-off”), random oscillations of on-off symptoms
  - major complication of levodopa is dyskinesia
- treatment of early PD: dopamine agonists, amantadine, MAOI
- adjuncts: dopamine agonists, MAOI, anticholinergics (especially if prominent tremors), COMT inhibitors
- surgical: thalamotomy, pallidotomy, deep brain stimulation (thalamic, pallidal, subthalamic)
- psychiatric

Other Parkinsonian Disorders
- dementia/NCD with Lewy bodies (see Behavioural Neurology, N21)
- progressive supranuclear palsy: tauopathy with limited vertical gaze (classically downgaze), early falls, axial rigidity and akinesia, dysarthria, and dysphagia
- corticobasal degeneration: tauopathy with varied presentations but classically presents with unilateral parkinsonism, dystonia/myoclonus, apraxia ± “alien limbs” phenomenon; may also present as progressive non-fluent aphasia
- multiple system atrophy: synucleinopathy presenting as either cerebellar predominant (previously olivopontocerebellar atrophy or OPCA) or parkinsonism predominant (previously nigrostriatal degeneration); both are associated with early autonomic dysfunction (previously Shy-Drager syndrome)
- vascular parkinsonism: multi-infarct presentation with lower body parkinsonism

Huntington’s Disease
Etiology and Pathogenesis
- genetics: autosomal dominant CAG repeats (with anticipation) in Huntington’s gene on Chromosome 4, which leads to accumulation of defective protein in neurons
- pathology: global cerebral atrophy, especially affecting the striatum, leading to increased activity of the direct pathway, and decreased activity of the indirect pathway

Risk Factors
- family history, male, head injury, rural living, exposure to certain neurotoxins
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Epidemiology
- North American prevalence 4-8/100,000
- mean age of onset 35-44 yr; but varies with degree of anticipation from 5-70 yr

Signs and Symptoms
- typical progression: insidious onset with clumsiness, fidgetiness, and irritability, progressing over 15 yr to frank dementia, psychosis, and chorea
  - dementia: progressive memory impairment and loss of intellectual capacity
  - chorea: begins as movement of eyebrows and forehead, shrugging of shoulders, and parkakinesia (pseudo-purposeful movement to mask involuntary limb jerking)
  - progresses to dance-like or ballism, and in late stage is replaced by dystonia and rigidity
  - mood changes: irritability, depression, anhedonia, impulsivity, bouts of violence

Investigations
- MRI: enlarged ventricles, atrophy of cerebral cortex and caudate nucleus
- genetic testing
  - expansion of the cytosine-adenine-guanine (CAG) trinucleotide repeats in the HTT gene
  - CAG repeats on chromosome 4p16.3 that encodes the protein huntingtin

Treatment
- no disease altering treatment
- psychiatric symptoms: antidepressants and antipsychotics
- chorea: neuroleptics and benzodiazepines
- dystonia: botulinum toxin

Dystonia

Epidemiology
- third most common movement disorder after Parkinson's disease and essential tremor

Clinical Features
- symptoms exacerbated by fatigue, stress, emotions; relieved by sleep or specific tactile/proprioceptive stimuli ('geste antagoniste', e.g. place hand on face for cervical dystonia)
- more likely to be progressive and generalize if younger onset or leg dystonia

Treatment
- local medical: botulinum toxin
- systemic medical: anticholinergics (benztropine), muscle relaxants (baclofen), benzodiazepines, dopamine antagonists (reserpine, neuroleptics); dopamine for dopa-responsive dystonia
- surgical: surgical denervation of affected muscle, stereotactic thalamotomy (unilateral dystonia), posterovenal pallidotomy

Tic Disorders

Definition
- a tic is a sudden, rapid, recurrent, nonrhythmic, stereotyped motor movement or vocalization
- common criteria
  - tics may wax and wane in frequency but have persisted for an extended period of time
  - onset before age 18 yr
  - disturbance is not attributable to the physiological effects of a substance or another medical condition

Clinical Classification
- **Tourette's disorder**: multiple motor and one or more vocal tics that have persisted for more than 1 yr since onset
- **persistent (chronic) motor or vocal tic disorder**: single or multiple motor or vocal tics (but not both motor and vocal) that have persisted for more than 1 yr since onset
- **provisional tic disorder**: single or multiple motor and/or vocal tics present for <1 yr since first tic onset
- **other specified or unspecified tic disorder**: symptoms characteristic of a tic disorder but do not meet full criteria

Motor vs. Vocal Tics
- simple tics tend to be of short duration (milliseconds)
- complex tics tend to be longer (seconds) and often include a combination of simple tics
- complex tics may often appear to be purposeful

Botulinum toxin (BOTOX®) acts by preventing ACh release at the neuromuscular junction.
• motor tics
  † simple: blinking, head jerking, shoulder shrugging, extension of the extremities
  † dystonic: bruxism (grinding teeth), abdominal tension, sustained mouth opening
  † complex: copropraxia (obscene gestures), echopraxia (imitate gestures), throwing, touching
• vocal tics
  † simple: blowing, coughing, grunting, throat clearing
  † complex: coprolalia (shout obscenities), echolalia (repeat others' phrases), palilalia (repeat own phrases)

Treatment
• dopamine blocker

Tourette’s Syndrome
(Gilles de la Tourette’s Syndrome)

Definition According to DSM 5
1. presence of both multiple motor and one or more vocal tics at some point during the illness, although not necessarily concurrently
2. tics may wax and wane in frequency but have persisted for more than 1 yr since first tic onset (with no tic-free periods greater than 3 mo)
3. onset is before age 18 yr
4. not due to effect of a substance or another medical condition

Epidemiology
• estimated prevalence among adolescents 3-8 per 1,000 school-age children; M:F = 2:1 to 4:1

Signs and Symptoms
• tics: wide variety that wax and wane in type and severity; can be voluntarily suppressed for some time but are preceded by unpleasant sensation that is relieved once tic is carried out
  † can be worsened by anxiety, excitement, and exhaustion; better during calm focused activities
• psychiatric: compulsive behaviour (associated with OCD and ADHD), hyperactive behaviour, ‘rages’, sleep-wake disturbances, learning disabilities

Treatment
• clonidine, clonazepam

Prognosis
• typically begins between ages 4-6
• peak severity occurs between ages 10-12, with a decline in severity during adolescence (50% are tic-free by 18 yr of age)
• tic symptoms, however, can manifest similarly in all age groups and across the lifespan

Cerebellar Disorders

Clinico-Anatomic Correlations
• vermis: trunk/gait ataxia
• cerebellar lobe (i.e. lateral): rebound phenomenon, scanning dysarthria, dysdiadochokinesia, dysmetria, nystagmus

Symptoms and Signs of Cerebellar Dysfunction
• nystagmus: observe during extraocular movement testing (most common is gaze-evoked nystagmus)
• dysarthria (ataxic): abnormal modulation of speech velocity and volume – elicit scanning/telegraphic/slurred speech on spontaneous speech (see CN X Vagus Nerve, N13)
• ataxia: broad-based, uncoordinated, lurching gait
• dysmetria: irregular placement of voluntary limb or ocular movement
• dysdiadochokinesia: impairment of rapid alternating movements (e.g. pronation – supination task)
• postural instability: truncal ataxia on sitting, titubation (rhythmic rocking of trunk and head), difficulty with tandem and broad-based gait
• intention tremor: typically orthogonal to intended movement, and increases as target is approached
• hypotonia: decreased resistance to passive muscular extension (occurs shortly after injury to lateral cerebellum)
• pendular patellar reflex: knee reflex causes pendular motion of leg (occurs after injury to cerebellar hemispheres)
• rebound phenomenon: overcorrection after displacement of a limb
• hypometric and hypermetric saccades
  † pendular reflexes at triceps

Differentiating Ataxia

<table>
<thead>
<tr>
<th>Vertebro</th>
<th>Cerebellar</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nystagmus/Vertigo</td>
<td>+ ± –</td>
<td>–</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>– ± –</td>
<td>–</td>
</tr>
<tr>
<td>Limb Ataxia</td>
<td>– + +</td>
<td>+ especially distal</td>
</tr>
<tr>
<td>Stance</td>
<td>Worsened with eyes closed</td>
<td>Poor with eyes open or closed</td>
</tr>
<tr>
<td>Vibration/Proprioception</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Ankle Reflexes</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>
Wernicke-Korsakoff Syndrome

- see Psychiatry, PS25
- note that alcohol can also cause a cerebellar ataxia separate from thiamine deficiency; this ataxia can be due to cerebellar atrophy or alcohol polyneuropathy

Cerebellar Ataxias

Congenital Ataxias
- early onset non-progressive ataxias associated with various syndromes as well as developmental abnormalities (e.g. Arnold-Chiari malformation, Dandy-Walker cysts)

Hereditary Ataxias
- autosomal recessive: includes Friedrich's ataxia, ataxia telangiectasia, vitamin E deficiency
  - Friedrich's ataxia: prevalence 2/100,000; onset between 8 and 15 yr
    - signs: gait and limb ataxia, weakness, areflexia, extensor plantar reflex, impaired proprioception and vibration, dysarthria
    - death in 10-20 yr from cardiomyopathy or kyphoscoliotic pulmonary restriction
- autosomal dominant: most commonly spinocerebellar ataxias (30 types, most due to CAG repeats)
  - signs: ataxia and dysarthria; ± myoclonus, chorea, polyneuropathy, pyramidal or extrapyramidal features, hyporeflexia, seizures, dementia

Acquired Ataxias
- neurodegeneration (e.g. multiple system atrophy)
- systemic: alcohol, celiac sprue, hypothyroidism, Wilson's, thiamine deficiency
- toxins: carbon monoxide, heavy metals, lithium, anticonvulsants, solvents
- vascular: infarct, bleed, basilar migraine
- autoimmune: MS, Miller-Fischer (GBS)

Vertigo

- see Otolaryngology, OT12

Gait Disturbances

Approach to Gait Disturbances

1. Characterization of the gait disturbance
   - posture, stride length, width between feet, height of step, stability of pelvis, symmetry, arm swing, elaborate/inconsistent movements, standing from sitting
2. Identification of accompanying neurologic signs
   - full neurological exam required (diagnosis often can be made by P/E alone)
3. Identify red flags
   - sudden onset, cerebellar ataxia, paresis (hemipara, para- or quadri-), bowel/bladder incontinence
4. Workup
   - based on etiology – requires blood work, neuroimaging, and urgent neurologist referral

Table 19. Types of Gait Disturbance

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual Loss</td>
<td>Broad based gait with tentative steps</td>
<td>Cataract surgery without lens replacement</td>
</tr>
<tr>
<td>Proopioceptive Loss</td>
<td>Sensory ataxia: wide-based with high stepping posture and positive Romberg</td>
<td>Demyelinating neuropathies, paraneoplastic syndrome, tabes dorsalis, MS, compressive myelopathy, B12 deficiency</td>
</tr>
<tr>
<td>Peripheral Vestibular Lesion</td>
<td>1. Vestibular ataxia</td>
<td>1. Tumour, trauma, infectious, Ménière’s disease</td>
</tr>
<tr>
<td></td>
<td>2. Disequilibrium</td>
<td>2. Ototoxic drugs</td>
</tr>
<tr>
<td>Peripheral Nerve Disorder</td>
<td>Steppage gait</td>
<td>Acquired/hereditary peripheral neuropathy, compressive peroneal neuropathy, L4-5 radiculopathy</td>
</tr>
<tr>
<td>Myopathies</td>
<td>Waddling gait: broad based, short stepped gait with pronounced lumbar lordosis, rotation of pelvis</td>
<td>Progressive muscular dystrophy</td>
</tr>
</tbody>
</table>
Table 19. Types of Gait Disturbance (continued)

<table>
<thead>
<tr>
<th>Location</th>
<th>Description</th>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyramidal/Corticospinal Tract</td>
<td>Unilateral: stroke (ischemic/hemorrhagic)</td>
<td>Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumour, combined spinal cord degeneration, MS, motor neuron disease</td>
</tr>
<tr>
<td>1. Unilateral</td>
<td>Spastic gait: spastic foot drop, circumduction, scissoring of legs or toe walking with bilateral circumduction</td>
<td></td>
</tr>
<tr>
<td>2. Bilateral</td>
<td>Bilateral: cervical spondylosis, cerebral palsy, spinal cord tumour, combined spinal cord degeneration, MS, motor neuron disease</td>
<td></td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>1. Parkinsonian gait: small paces, stooped posture, reduced armswing</td>
<td>Infarct, Huntington’s, Sydenham’s chorea, Wilson’s disease, SLE, neuroleptic medications, polycythemia vera, genetic dystonia</td>
</tr>
<tr>
<td>2. Choreic/hemiballistic/dystonic gait</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cerebellar Disorder</td>
<td>Cerebellar ataxic gait: wide-based without high stepping; veers to side of lesion</td>
<td>Primary and secondary neoplasm, toxins (alcohol), vitamin E deficiency, hypothyroid, hypoxia, hypoglycemia, paraneoplastic syndrome</td>
</tr>
<tr>
<td>Alcoholic gait</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Motor Neuron Disease

Amyotrophic Lateral Sclerosis (Lou Gehrig’s Disease)

Definition
- progressive neurodegenerative disease that causes UMN and LMN symptoms and is ultimately fatal

Etiology
- idiopathic (most), genetic (5-10% familial, especially SOD1 mutation, other: C9orf72, TARDBP)

Pathology
- disorder of anterior horn cells of spinal cord, cranial nerve nuclei, and corticospinal tract

Epidemiology
- 5/100,000; incidence increases with age

Signs and Symptoms
- limb motor symptoms: segmental and asymmetrical UMN and LMN symptoms
- bulbar findings: dysarthria (flaccid or spastic), dysphagia, tongue atrophy and fasciculations, facial weakness and atrophy
- pseudobulbar affect, frontotemporal dementia (up to 10%)
- sparing of sensation, ocular muscles, and sphincters

Investigations
- EMG: chronic denervation and reinnervation, fasciculations
- NCS: to rule out peripheral neuropathy (i.e. multifocal motor neuropathy with conduction block)
- CT/MRI: to rule out cord disease/compression

Treatment
- riluzole (modestly slows disease progression)
- symptomatic relief
  - spasticity/cramping: baclofen, tizanidine (Zanaflex®), regular exercise, and physical therapy
  - sialorrhea: TCA (i.e. amitriptyline), sublingual atropine drops, parotid/submandibular Botox® (rare)
  - pseudobulbar affect: dextromethorphan/quinidine, TCA, SSRI
- non-pharmacologic: high caloric diet, ventilatory support (especially BiPAP), early nutritional support (i.e. PEG tube), rehabilitation (PT, OT, SLP), psychosocial support

Prognosis
- median survival 3 yr; death due to respiratory failure

Other Motor Neuron Diseases

- degenerative
  - progressive muscular atrophy (progressive bulbar palsy): only LMN symptoms with asymmetric weakness, later onset than ALS, 5-10% of patients in ALS centres
  - primary lateral sclerosis (progressive pseudobulbar palsy): UMN symptoms, later onset, not fatal with variable disability; 5-10% of patients in ALS centres
  - spinal muscular atrophy: pediatric disease with symmetric LMN symptoms
- infectious
  - post-polio syndrome: residual asymmetric muscle weakness, atrophy
- acquired
  - multifocal motor neuropathy: conduction block on NCS, asymmetric LMN symptoms, ± anti-GM1, treatable with IVIG
Peripheral Neuropathies

Diagnostic Approach to Peripheral Neuropathies

1. differentiate: motor vs. sensory vs. autonomic vs. mixed
2. pattern of deficit: symmetry; focal vs. diffuse; upper vs. lower limb; cranial nerve involvement
3. temporal pattern: acute vs. chronic; relapsing/remitting vs. constant vs. progressive
4. history: PMH, detailed FHx, exposures (e.g. insects, toxins, sexual, travel), systemic symptoms
5. detailed peripheral neuro exam: LMN findings, differentiate between root and peripheral nerves, cranial nerves, respiratory status

Classification

- monoradiculopathy: dermatomal deficit due to single nerve root lesion
  - due to disc herniation or root compression causing radicular pain
  - little tactile anesthesia, as dermatomes overlap
- polyradiculopathy: multiple dermatome deficits due to multiple nerve root lesions
  - one type is cauda equina syndrome (lumbosacral roots)
- plexopathy: deficit matching distribution of a nerve plexus
  - brachial plexopathy
    - upper (C5-C7): LMN sx of shoulder and upper arm muscles (Erb's palsy)
    - lower (C8-T1): LMN sx and sensory sx of forearm and hand (Klumpke's palsy)
  - DDx: trauma, idiopathic neuritis, tumour infiltration, radiation, thoracic outlet syndrome
    - (i.e. cervical rib)
- lumbosacral plexopathy (rare, especially unilateral)
  - DDx: idiopathic neuritis, infarction (i.e. DM), compression

- mononeuropathy: single nerve deficit
  - carpal tunnel syndrome (most common); compression of median nerve at wrist
    - symptoms: wrist pain, paresthesia first 3 and ½ digits, ± radiation to elbow, worse at night
    - signs: Tinel’s sign, Phalen’s test, thenar muscle wasting, sensory deficit
    - EMG and NCS: slowing at wrist (both motor and sensory)
  - etiology: entrapment, pregnancy, DM, gammapathy, rheumatoid arthritis, thyroid disease
  - Bell’s palsy (most common cranial neuropathy): see Otolaryngology, OT23
    - other less common mononeuropathies due to entrapment/compression: ulnar (compression at elbow), median (at pronator teres), radial (at spiral groove of humerus), obturator (from childbirth), peroneal (due to crossing legs or surgical positioning), posterior tibial (tarsal canal)

- mononeuropathy multiplex: deficit affecting multiple discrete nerves (asymmetric)
  - must rule out vasculitis or collagen vascular disease

- polyneuropathy: symmetrical distal stocking-glove pattern
  - symmetrical distal sensorimotor deficit affecting longest fibres first (stocking-glove distribution), hypotonia; progression of dysesthesia early and weakness later
  - etiology: DM (most common), renal disease, substances, toxins, genetics, SLE, HIV, leprosy, alcohol, B12 deficiency, uremia

- chronic inflammatory demyelinating polyneuropathy (CIDP)
  - chronic relapsing sensorimotor polyneuropathy with increase protein in CSF and demyelination (shown on EMG/NCS)
    - course is fluctuating, in contrast with the acute onset of GBS
  - treatment: first-line is prednisone; alternatives are plasmapheresis, IVIG, and azathioprine

Table 20. Differential Diagnosis of Symmetric Polyneuropathy

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Mechanism</th>
<th>Course</th>
<th>Modalities</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatology, RH19</td>
</tr>
<tr>
<td>LAM</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatology, RH11</td>
</tr>
<tr>
<td>RA</td>
<td>Ischemic</td>
<td>Chronic</td>
<td>S/M</td>
<td>see Rheumatology, RH8</td>
</tr>
<tr>
<td>Infectious</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/A</td>
<td>HIV serology</td>
</tr>
<tr>
<td>Leprosy</td>
<td>Infiltrative</td>
<td>Chronic</td>
<td>S/A</td>
<td>Leprosy serology</td>
</tr>
<tr>
<td>Lyme</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>M</td>
<td>Nerve biopsy</td>
</tr>
<tr>
<td>Lyme serology</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immune</td>
<td>Demyelination</td>
<td>Acute</td>
<td>M</td>
<td>LP († protein; no † cells)</td>
</tr>
<tr>
<td>CIDP</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>LP († protein)</td>
</tr>
<tr>
<td>Heraleditary</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Paraneoplastic</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Paraneoplastic antibodies</td>
</tr>
<tr>
<td>Myeloma</td>
<td>Axonal/demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>SPEP</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Axonal</td>
<td>Chronic</td>
<td>M</td>
<td>Skeletal bone survey</td>
</tr>
<tr>
<td>Monoclonal</td>
<td>Demyelination</td>
<td>Chronic</td>
<td>S/M</td>
<td>Bone marrow biopsy</td>
</tr>
<tr>
<td>gammopathy</td>
<td></td>
<td></td>
<td></td>
<td>Borderline biopsy</td>
</tr>
</tbody>
</table>
Table 20. Differential Diagnosis of Symmetric Polyneuropathy (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Mechanism</th>
<th>Course</th>
<th>Modalities</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxin</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>GGT, MCV</td>
</tr>
<tr>
<td></td>
<td>EtOH</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td>Heavy metals</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td>Drug levels</td>
</tr>
<tr>
<td>Medications</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
<td></td>
</tr>
<tr>
<td>Metabolic</td>
<td>DM</td>
<td>Ischemic/axonal</td>
<td>Chronic</td>
<td>S/A</td>
</tr>
<tr>
<td></td>
<td>Hypothyroidism</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/M</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
<td>Axonal</td>
<td>Chronic</td>
<td>S/A</td>
</tr>
<tr>
<td>Nutritional</td>
<td>B12 deficiency</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S/M</td>
</tr>
<tr>
<td>Other</td>
<td>Porphyria</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>M</td>
</tr>
<tr>
<td></td>
<td>Amyloid</td>
<td>Axonal</td>
<td>Sub-acute</td>
<td>S</td>
</tr>
</tbody>
</table>

A = autonomic; CIDP = chronic inflammatory demyelinating polyneuropathy; GGT = gamma-glutamyl transferase; HMSN = hereditary motor sensory neuropathy; M = motor; OGTT = oral glucose tolerance test; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; S = sensory; SLE = systemic lupus erythematosus; SPEP = serum protein electrophoresis

Guillain-Barré Syndrome
- **definition:** acute rapidly evolving demyelinating inflammatory polyneuropathy that often starts in the distal lower limbs and ascends
- **etiology**
  - autoimmune attack and damage to peripheral nerve myelin
  - sometimes preceded by viral/bacterial infections
- **signs and symptoms**
  - sensory: distal and symmetric paresthesias, loss of proprioception and vibration sense, neuropathic pain
  - motor: weakness starting distally in legs, areflexia
  - autonomic: blood pressure dysregulation, arrhythmias, bladder dysfunction
- **investigations**
  - CSF: albuminocytologic dissociation (high protein, normal WBC)
  - EMG/NCS: conduction block, differential or focal (motor > sensory) slowing, decreased F-wave, sural sparing
- **subtypes**
  1. acute inflammatory demyelinating polyneuropathy (AIDP)
  2. acute motor-sensory axonal neuropathy (AMSAN)
  3. acute motor axonal neuropathy (AMAN)
- **treatment**
  - IVIG or plasmapheresis, ± pain management, monitor vitals and vital capacity
- **prognosis**
  - peak of symptoms at 2-3 wk, resolution at 4-6 wk
  - 5% mortality (higher if require ICU); up to 15% have permanent deficits

Neuromuscular Junction Diseases

Clinical Approach to Disorders of the Neuromuscular Junction

Table 21. Common Disorders of the Neuromuscular Junction

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Myasthenia Gravis</th>
<th>Lambert-Eaton</th>
<th>Botulism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular/Bulbar Paresis</td>
<td>+</td>
<td>-</td>
<td>+ (early)</td>
</tr>
<tr>
<td>Limb Weakness</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Fatigability</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Post-Exercise Enhancement</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reflexes</td>
<td>N</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Anticholinergic Sx</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sensory Sx</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Associated Conditions</td>
<td>Thymoma</td>
<td>Small cell carcinoma</td>
<td>GI S&amp;S</td>
</tr>
<tr>
<td>Repetitive EMG Stimulation</td>
<td>Decremental response</td>
<td>Incremental response</td>
<td>↑ (rapid stimulation) ↓ (slow stimulation)</td>
</tr>
</tbody>
</table>
**Myasthenia Gravis**

**Etiology and Pathophysiology**
- progressive autoimmune disorder due to anti-AChR antibodies, resulting in early saturation at the NMJ and inadequate muscle activation with increasing nerve stimulation
- 15% of patients with MG have associated thymic neoplasia, 85% have thymic hyperplasia

**Epidemiology**
- bimodal age of onset – 20s (mostly women) and 60s (mostly men)

**Signs and Symptoms**
- see Table 21
- fatigable, symmetric or asymmetric weakness without reflex changes, sensory changes, or coordination abnormalities
- ocular (diplopia/ptosis), bulbar (dysarthria/dysphagia), and/or proximal limb weakness
- symptoms may be exacerbated by infection, pregnancy, menses, and various drugs
- respiratory muscle weakness may lead to respiratory failure

**Investigations**
- edrophonium (Tensilon®) test
  - assess for improvement over 2 min following edrophonium injection
- EMG
  - repetitive stimulation → decremental response
  - single fibre electromyography shows increased jitter (80-100% sensitivity)
  - spirometry – forced vital capacity may be used to monitor adequacy of respiratory effort over time
- anti-acetylcholine receptor antibody assay (70-80% sensitivity)
- CT/MRI to screen for thymoma/thymic hyperplasia

**Treatment**
- thymectomy
  - 85% of patients show improvement or remission
- symptomatic relief
  - acetylcholinesterase inhibitors (e.g. pyridostigmine)
  - does not affect primary pathologic process so rarely results in control of disease when used alone
- immunosuppression
  - steroids are mainstay of treatment (70-80% remission rate)
  - azathioprine, cyclophosphamide, and mycophenolate as adjuncts or as steroid sparing therapy
- short-term immunomodulation (for crises)
  - IVIG and plasmapheresis

**Prognosis**
- 30% eventual spontaneous remission
- with treatment, life expectancy is equal to that of a person without MG, but quality of life may vary

**Lambert-Eaton Myasthenic Syndrome**

**Etiology and Pathophysiology**
- autoimmune disorder due to antibodies against presynaptic voltage-gated calcium channels, causing decreased ACh release at the NMJ
- 50-66% are associated with small cell carcinoma of the lung

**Signs and Symptoms**
- see Table 21
- weakness of skeletal muscles without sensory or coordination abnormalities
- reflexes are diminished or absent, but increase after active muscle contraction
- bulbar and oculomotor muscles affected in 25% (vs. 90% in MG)
- prominent anticholinergic autonomic symptoms (dry mouth > impotence > constipation > blurred vision)

**Investigations**
- edrophonium test (see Myasthenia Gravis, N40) → no response
- EMG
  - rapid (>10 Hz) repetitive stimulation → incremental response
  - post-exercise facilitation → an incremental response with exercise
  - screen for malignancy, especially small cell lung cancer

**Figure 22. Myasthenia gravis**

**Figure 23. Lambert-Eaton myasthenic syndrome (LEMS)**
Treatment
- tumour removal
- acetylcholine modulation
  - increased acetylcholine release (3,4-diaminopyridine)
  - decreased acetylcholine degradation (pyridostigmine)
- immunomodulation
  - steroids, plasmapheresis, IVIG

Botulism

Etiology and Pathophysiology
- caused by a toxin produced by spores of *Clostridium botulinum* bacteria, which is found in soil and water throughout the world
- bacteria can enter the body through wounds or by ingesting improperly preserved foods
- infantile botulism is the most common form, and is usually from ingestion of honey or corn syrup

Signs and Symptoms
- occur 6-48 h after ingestion
- difficulty with convergence, ptosis, paralysis of extraocular muscles
- dilated, poorly reactive pupils
- other autonomic dysfunction: jaw weakness, dysarthria, dysphagia
- spreads to trunk and limbs
  - abdominal cramps with nausea and vomiting
  - symmetric weakness with paralysis and absent/decreased deep tendon reflexes
  - anticholinergic symptoms: dry mouth, constipation, urinary retention
- rarely respiratory distress, potentially advancing to respiratory failure
  - pattern of paresis often starts with GI symptoms (constipation, early satiety), then paresis of extraocular muscles, then dysphagia, then limbs/respiratory involvement; all associated with dry mouth

Investigations
- blood test for toxin
- stool culture

Treatment
- botulinum anti-toxin – good prognosis with prompt treatment
- supportive therapy as required

Myopathies

Clinical Approach to Muscle Diseases

Table 22. Myopathies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Key Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polymyositis</td>
<td>Myalgias</td>
<td>↑ CK</td>
</tr>
<tr>
<td></td>
<td>Pharyngeal involvement</td>
<td>Biopsy; endomyosial infiltrates; necrosis</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>Myalgias</td>
<td>↑ CK</td>
</tr>
<tr>
<td></td>
<td>Characteristic rashes</td>
<td>Biopsy; perifascicular atrophy</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>See Respirology, R14</td>
<td>ACE level</td>
</tr>
<tr>
<td></td>
<td>Weak quadriceps and deep finger flexors</td>
<td>Biopsy: granulomas</td>
</tr>
<tr>
<td>Inclusion body myositis</td>
<td>See Endocrinology, E20</td>
<td>TSH, serum cortisol, calcium panel</td>
</tr>
<tr>
<td><strong>Endocrine</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid (↑ or ↓)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cushing’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parathyroid (↑ or ↓)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Toxic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td>Medication or toxin history</td>
<td>Toxicology screen</td>
</tr>
<tr>
<td>Critical illness myopathy</td>
<td>Hx steroids and nondepolarizing paralyzing agents</td>
<td>Biopsy: selective loss of thick myosin filaments</td>
</tr>
<tr>
<td></td>
<td>Failure to wean from ventilation</td>
<td></td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parasitic, bacterial, or viral</td>
<td>Myalgias</td>
<td>↑ myoglobin</td>
</tr>
<tr>
<td></td>
<td>Inflammatory myopathy</td>
<td></td>
</tr>
</tbody>
</table>

Myopathies are characterized by prominent symmetric proximal weakness and absent sensory changes

Good Questions to Assess Proximal Weakness
- Legs: climbing stairs, stand from sit
- Arms: reach above head, wash hair
Table 22. Myopathies (continued)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Key Clinical Features</th>
<th>Key Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hereditary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dystrophy</td>
<td>Early onset (Duchenne and Becker)</td>
<td>Dystrophin analysis: absent</td>
</tr>
<tr>
<td>Duchenne</td>
<td>Progressive proximal muscle weakness</td>
<td>Dystrophin analysis: abnormal</td>
</tr>
<tr>
<td>Becker</td>
<td>Calf pseudohypertrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Myotonic dystrophy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Distal myopathy</td>
<td>Genetic testing</td>
</tr>
<tr>
<td>Metabolic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McArdle’s</td>
<td>Exercise-related myalgias, cramping, and myoglobinuria</td>
<td>↑ lactate</td>
</tr>
<tr>
<td>Periodic</td>
<td></td>
<td>↑ serum/urinary myoglobin</td>
</tr>
<tr>
<td>Paralysis</td>
<td>Episodic weakness</td>
<td>post-exercise</td>
</tr>
<tr>
<td>“Channelopathy”</td>
<td>Normal between attacks</td>
<td></td>
</tr>
<tr>
<td>MERRF</td>
<td>Myoclonus, generalized seizures, dementia, myopathy</td>
<td>Biopsy: ragged red fibres</td>
</tr>
<tr>
<td>Mitochondrial</td>
<td></td>
<td>Increased lactate</td>
</tr>
<tr>
<td>MELAS</td>
<td>Pediatric onset, stroke-like symptoms, episodic vomiting,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dementia, myopathy</td>
<td></td>
</tr>
<tr>
<td>Kearns Sayre</td>
<td>Progressive ophthalmoplegia, retinal pigment degeneration,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>cardiac conduction abnormalities</td>
<td></td>
</tr>
</tbody>
</table>

MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = mitochondrial encephalomyopathy with ragged red fibres

Polymyositis/Dermatomyositis

- see Rheumatology, RH15

Myotonic Dystrophy

Etiology and Pathophysiology
- unstable trinucleotide (CTG) repeat in DMK gene (protein kinase) at 19q13.3, number of repeats correlates with severity of symptoms
- autosomal dominant

Epidemiology
- most common adult muscular dystrophy
- prevalence 3-5/100,000

Signs and Symptoms
- appearance: ptosis, bifacial weakness, frontal baldness (including women), triangular face giving a drooping/dull appearance
- physical exam
  - distribution of weakness: distal weaker than proximal (in contrast to other myopathies), steppage gait
  - myostonia: delayed relaxation of muscles after exertion (elicit by tapping on thenar muscles with hammer)
  - cardiac: 90% have conduction defects (1st heart block; atrial arrhythmias)
  - respiratory: hypoventilation 2nd to muscle weakness
  - ocular: subcapsular cataracts, retinal degeneration, decreased intraocular pressure
  - other: DM, infertility, testicular atrophy
- EMG: subclinical myotonia – long runs with declining frequency and amplitude

Treatment and Prognosis
- no cure, progressive, death usually around 50 yr
- management of myotonia: phenytoin

Duchenne and Becker Muscular Dystrophy

- see Pediatrics, P45
Pain Syndromes

Approach to Pain Syndromes

Definitions
• nociceptive pain: pain arising from normal activation of peripheral nociceptors
• neuropathic pain: pain arising from direct injury to neural tissue, bypassing nociceptive pathways
• spontaneous pain: unprovoked burning, shooting, or lancinating pain
• paresthesia: spontaneous abnormal non-painful sensation (e.g. tingling)
• dyesthesias: evoked pain with inappropriate quality or excessive quantity
• loss of sensation
• hypesthesias: loss of pain sensation
• hyperalgesia: an exaggerated pain response to a noxious stimulus
• allodynia: a dyesthetic response to a non-noxious stimulus

Non-Pharmacological Management
• physical (PT, acupuncture, chiropractic manipulation, massage)
• psychoeducational (CBT, family therapy, education, psychotherapy)

Medical Pain Control
• combination multi-modal therapy is important
• primary analgesics: acetaminophen, NSAIDs (often used for soft tissue injuries, strains, sprains, headaches, and arthritis), opiates
• adjuvants: antidepressants (TCAs, SSRIs), anticonvulsants (gabapentin, carbamazepine, pregabalin), baclofen, sympatholytics (phenoxybenzamine), \( \alpha_2 \)-adrenergic agonists (clonidine)

Surgical Pain Control
• peripheral ablation: nerve blocks, facet joint denervation
• direct delivery: implantable morphine pump
• central ablation: stereotactic thalamotomy, spinal tractotomy, or dorsal root entry lesion
• DBS or dorsal column stimulation

Neuropathic Pain

Definition
• pain resulting from a disturbance of the central or peripheral nervous system

Symptoms and Signs
• hyperalgesia/allodynia
• subjectively described as burning, heat/cold, pricking, electric shock, perception of swelling, numbness (i.e. stocking/sock distribution)
• can be spontaneous or stimulus evoked
• distribution may not fall along classical neuro-anatomical lines
• associated issues: sleep difficulty, anxiety/stress/mood alteration

Causes of Neuropathic Pain
• sympathetic
  • complex regional pain syndrome
• central: abnormal CNS activity
  • phantom limb, post spinal cord injury, post stroke, MS
• non-sympathetic: damage to peripheral nerves
• systemic disease: DM, thyroid disease, renal disease, rheumatoid arthritis
• nutritional/toxicity: alcoholism, pernicious anemia, chemotherapy
• infectious: post-herpetic, HIV
• trauma/compression: nerve entrapment, trigeminal neuralgia, post-surgical, nerve injury, cervical/lumbar radiculopathy, plexopathy

Treatment
• identify/treat underlying cause
• pharmacotherapy
  • Stepwise approach (Canadian Pain Society, 2007): TCA, anticonvulsants, SNRI, topical lidocaine, long acting opiate (caution), tramadol
  • other: capsaicin cream, intrathecal opioid, or clonidine, botulinum toxin injection, nerve block
• common non-pharmacologic therapies
  • neuropsychiatry: CBT, psychotherapy
  • rehabilitation: physiotherapy
  • complementary and alternative medicine: acupuncture, meditation, massage therapy, traditional Chinese medicine
• surgical therapies: dorsal column neurostimulator, DBS (thalamus)
Trigeminal Neuralgia

Clinical Features
• recurrent episodes of sudden onset, excruciating unilateral paroxysmal shooting “electric” pain in trigeminal root territory (V3>V2>V1)
• may have normal sensory exam
• pain lasts seconds/minutes over days/weeks; may remit for wk/mo
• triggers: touching face, eating, talking, cold wind, shaving, applying make-up

Etiology
• classic TN: idiopathic
• secondary TN: compression by tortuous blood vessel (superior cerebellar artery), cerebellopontine angle tumour (5%), MS (5%)

Epidemiology
• F>M; usually middle-aged and elderly

Diagnosis
• clinical diagnosis
• investigate for secondary causes, which are more likely if bilateral TN or associated sensory loss
  ▪ MRI to rule out structural lesion, MS, or vascular lesion

Treatment
• first line: carbamazepine or oxcarbazepine
• second line: baclofen or lamotrigine
• narcotics not generally recommended
• if medical treatment fails: trigeminal ganglion percutaneous technique, gamma knife, invasive percutaneous denervation (radiofrequency/glycerol), percutaneous balloon microcompression, microvascular decompression

Postherpetic Neuralgia

Clinical Features
• pain persisting in the region of a cutaneous outbreak of herpes zoster
• constant deep ache or burning, intermittent spontaneous lancinating/jabbing pain, allodynia
• distribution: thoracic, trigeminal, cervical > lumbar > sacral
• associated impaired sleep, decreased appetite, decreased libido

Etiology and Pathogenesis
• destruction of the sensory ganglion neurons (e.g. dorsal root, trigeminal, or geniculate ganglia) secondary to reactivation of herpes zoster infection

Epidemiology
• incidence in those with zoster increases with age (2% in <60 yr, 19% in >70 yr)
• risk factors: older age, greater acute pain, greater rash severity

Prevention
• varicella zoster vaccine (Varivax®) in childhood reduces incidence of varicella zoster
• herpes zoster vaccine (Zostavax®) reduces incidences of shingles, PHN, and other herpetic sequel (currently recommended in Canada for those >60 yr old)

Treatment
• medical: TCA (i.e. amitriptyline), anti-convulsants (i.e. pregabalin, gabapentin), analgesia (i.e. opiates, lidocaine patch), intrathecal methylprednisolone, topical capsaicin
  ▪ early treatment of acute herpes zoster with antivirals (acyclovir; longer-acting famciclovir and valacyclovir more effective)
  ▪ treatment of herpes zoster with corticosteroids DOES NOT decrease PHN
• surgical: spinal tractotomy, dorsal root entry zone lesion, DBS of thalamus

Painful Diabetic Neuropathy

• see Endocrinology, E13

Approach
• determine if pain is neuropathic or vascular
• more likely neuropathic if
  ▪ feet > calves
  ▪ sharp/tingling pain
  ▪ pain present at rest and improves with walking
Treatment
- Level A: pregabalin
- Level B: venlafaxine, duloxetine, amitriptyline, gabapentin, valproate, rarely opioids, capsaicin

**Complex Regional Pain Syndromes**

**Clinical Features**
- presence of an initiating noxious event (MI, stroke)
- continuing pain, allodynia, or hyperalgesia with pain disproportionate to inciting event
- evidence during the course of symptoms of edema, changes in skin blood flow or abnormal vasomotor activity
- absence of conditions that would otherwise account for degree of pain and dysfunction
- other features can include edema, osteoporosis, hyperhidrosis, hair loss, fascial thickening

**Classification**
- CRPS type I (reflex sympathetic dystrophy): minor injuries of limb or lesions in remote body areas precede onset of symptoms
- CRPS type II (causalgia): injury of peripheral nerves precedes the onset of symptoms

**Investigations**
- trial of differential neural blockade may be helpful in diagnosis
- autonomic testing (evidence of sympathetic dysfunction)
- bone scan, plain radiography, MRI

**Prevention**
- early mobilization after injury/infarction

**Treatment**
- goal of treatment: to facilitate function
- conservative treatment: education, support groups, PT/OT, smoking cessation
- medical: topical capsaicin, TCA, NSAID, tender point injections with corticosteroid/lidocaine, gabapentin/pregabalin/lamotrigine, calcitonin or bisphosphonates, oral corticosteroids
- surgical: paravertebral sympathetic ganglion blockade
- refer to pain management clinic

**Headache**

- see Emergency Medicine, ER23 and Family Medicine, FM33

**Clinical Approach**
- history
  - pain characteristics: onset, frequency, duration, intensity, location, radiation, other specific features (e.g. worse in AM, worse with bending/cough/Valsalva)
  - associated symptoms: visual changes, change in mental status, nausea/vomiting, fever, meningismus, photophobia, phonophobia, TMJ popping/clicking, jaw claudication, neurological symptoms
  - precipitating/alleviating factors (triggering factors, analgesics), medications (especially nitrates, CCBs, NSAIDs, anticoagulants), PMH, FHx
  - red flags (possible indications for CT scan/further investigation): new-onset headache (especially if age <5 or >50), quality worse/different than previous headaches, sudden and severe (‘thunderclap’), immunocompromised, fever, focal neurological deficits, trauma
- physical exam
  - vitals (including BP and temp), Kernig’s/Brudzinski’s, MSK examination of head and neck
  - HEENT: fundi (papilledema, retinal hemorrhages), red eye, temporal artery tenderness, sinus palpation, TMJ
  - full neurological exam (including LOC, orientation, pupils (symmetry), and focal neurological deficits)
  - red flags: papilledema, altered LOC, fever, meningismus, focal neurological deficits, signs of head trauma

**Classification**
- primary
  - tension, migraine, cluster, other autonomic cephalgias
- secondary
  - cervical OA, TMJ syndrome, SAH, ICH, stroke, venous sinus thrombosis, meningitis/encephalitis, trauma, increased ICP (space-occupying lesion, malignant HTN or pseudotumour cerebri), temporal arteritis, sinusitis, acute-angle closure glaucoma, pre-eclampsia, post LP, drugs/toxins (e.g. nitroglycerin use and analgesia withdrawal); all can be associated with serious morbidity or mortality
Table 23. Headaches – Selected Primary Types

<table>
<thead>
<tr>
<th>Tension-Type Migraine Cluster</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
</tr>
<tr>
<td>70%</td>
</tr>
<tr>
<td>Age of Onset</td>
</tr>
<tr>
<td>Sex Bias</td>
</tr>
<tr>
<td>Family History</td>
</tr>
<tr>
<td>Location</td>
</tr>
<tr>
<td>Nuchal-occipital</td>
</tr>
<tr>
<td>Fronto-temporal</td>
</tr>
<tr>
<td>Duration</td>
</tr>
<tr>
<td>Onset/Course</td>
</tr>
<tr>
<td>Quality</td>
</tr>
<tr>
<td>Severity</td>
</tr>
<tr>
<td>Triggers/Provoking</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Noise</td>
</tr>
<tr>
<td>Hunger</td>
</tr>
<tr>
<td>Sleep deprivation</td>
</tr>
<tr>
<td>Palliating</td>
</tr>
<tr>
<td>Associated Sx</td>
</tr>
<tr>
<td>Management</td>
</tr>
<tr>
<td>• Psychological counseling</td>
</tr>
<tr>
<td>• Physical modalities</td>
</tr>
<tr>
<td>e.g. heat, massage</td>
</tr>
<tr>
<td>Pharmacological</td>
</tr>
<tr>
<td>• Simple analogics</td>
</tr>
<tr>
<td>• Tricyclic antidepressants</td>
</tr>
<tr>
<td>3. Propranolol</td>
</tr>
<tr>
<td>Acute Rx</td>
</tr>
<tr>
<td>Evidence</td>
</tr>
<tr>
<td>Contraindications</td>
</tr>
<tr>
<td>Side Effects</td>
</tr>
<tr>
<td>Beta-blockers</td>
</tr>
<tr>
<td>Metoprolol</td>
</tr>
<tr>
<td>TCA</td>
</tr>
<tr>
<td>Noriptryline</td>
</tr>
<tr>
<td>* Avoid in elderly</td>
</tr>
<tr>
<td>CCBs</td>
</tr>
<tr>
<td>Verapamil</td>
</tr>
<tr>
<td>AED</td>
</tr>
<tr>
<td>Topiramate + folic acid</td>
</tr>
<tr>
<td>acid supplement</td>
</tr>
<tr>
<td>Topiramate</td>
</tr>
<tr>
<td>Polypharmacy</td>
</tr>
</tbody>
</table>

Table 24. Prophylactic Management of Migraine Headaches

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Evidence</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-blockers</td>
<td>Propranolol</td>
<td>A</td>
<td>Asthma, DM (mask hypoglycemia)</td>
<td>Fatigue</td>
</tr>
<tr>
<td></td>
<td>Timolol</td>
<td>A</td>
<td>Asthma, DM (mask hypoglycemia)</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Metoprolol</td>
<td>B</td>
<td>CHF</td>
<td>Light-headedness</td>
</tr>
<tr>
<td>TCA</td>
<td>Amitriptyline</td>
<td>A</td>
<td>Heart disease, glaucoma</td>
<td>Sedation</td>
</tr>
<tr>
<td>Noriptryline</td>
<td>C</td>
<td>Heart disease, glaucoma</td>
<td>Sedation</td>
<td></td>
</tr>
<tr>
<td>CCBs</td>
<td>Flunarizine</td>
<td>A</td>
<td>Depression, obesity</td>
<td>Weight gain, depression, PD (rare)</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
<td>B</td>
<td>Heart disease</td>
<td>Weight gain (4.5-9 kg), constipation</td>
</tr>
<tr>
<td>AED</td>
<td>Valproate</td>
<td>A</td>
<td>Liver, renal, pancreatic disease</td>
<td>Weight gain, tremor, ataxia, teratogenic: neural tube defect</td>
</tr>
<tr>
<td>Topiramate + folic acid</td>
<td>A</td>
<td>Renal disease</td>
<td>Paresthesia, weight loss, cogitive: memory loss, difficulty concentrating, renal stone (rare)</td>
<td></td>
</tr>
</tbody>
</table>

Table 25. Headaches – Selected Serious but Rare Secondary Types

<table>
<thead>
<tr>
<th>Meningeal Irritation</th>
<th>Increased ICP</th>
<th>Temporal Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of Onset</td>
<td>Any age</td>
<td>Any age</td>
</tr>
<tr>
<td>Location</td>
<td>Generalized</td>
<td>Any age</td>
</tr>
<tr>
<td>Onset/Course</td>
<td>Meningitis: hours-days</td>
<td></td>
</tr>
<tr>
<td>SAH: thunderclap onset</td>
<td>Gradual; worse in AM</td>
<td></td>
</tr>
<tr>
<td>Severity</td>
<td>Severe</td>
<td>Severe</td>
</tr>
<tr>
<td>Provoking</td>
<td>Lying down</td>
<td>Jaw claudication</td>
</tr>
<tr>
<td></td>
<td>Valsalva</td>
<td>Head low</td>
</tr>
<tr>
<td></td>
<td>Head low</td>
<td>Exertion</td>
</tr>
<tr>
<td>Associated Sx</td>
<td>Neck stiffness</td>
<td>Polymyalgia rheumatica</td>
</tr>
<tr>
<td></td>
<td>Photophobia</td>
<td>Visual loss</td>
</tr>
<tr>
<td></td>
<td>Focal deficits (e.g. CN palsies)</td>
<td>Decreased level of consciousness</td>
</tr>
</tbody>
</table>

Acute and Preventive Pharmacologic Treatment of Cluster Headache

Neurology 2012;75:463-473

Study: Meta-analysis of prospective, double-blind, RCTs of pharmacologic agents for prevention or treatment of CH.

Results: 27 trials were included. Sumatriptan 6 mg SC, zolmitriptan nasal spray 5-10 mg, and 100% oxygen 6-12 L/min received Level A recommendation for acute treatment. For prevention, Level B recommendations were given for intranasal xenon oxide 100 μg daily and subcutaneous steroids injections.

Conclusion: Sumatriptan, zolmitriptan, and mid flow oxygen are effective acute treatments for CH.

Anticonvulsants in Migraine Prophylaxis

Cochrane DB Syst Rev 2009;3:CD003226

Study: Meta-analysis of prospective, controlled trials of anticonvulsant drugs in migraine headache prophylaxis.

Results: Twenty-three studies (n=2,927) were included. Anticonvulsants reduce migraine frequency by 3.3 attacks per 28 days compared to placebo and double the number of patients for whom migraine frequency is reduced by 50% (RR=2.25, NNT=3.9). Valproate and topiramate are better than placebo, while clobazam, acetazolamide, lamotrigine, and vigabatrin are not. Clinically important adverse events were associated with valproate and topiramate with NNT 7.0-18.8 and 2.4-31.2, respectively.

Conclusion: Anticonvulsants are effective in reducing migraine frequency and reasonably well-tolerated. Valproate and topiramate are the two most studied but further studies of head-to-head comparisons between agents is needed.

The Rational Clinical Examination: Does this Patient with Headache have a Migraine or Need Neuroimaging?

JAMA 2006;296:1274-1283

Does this patient with headache have a migraine? The most useful panel of questions for diagnosing migraine is summarized by the POUNDing mnemonic:

P – Pulsatile quality
O – Onset – duration of 4-72 h
D – Disturbing intensity
U – Unilateral location
N – Nausa or vomiting
D – Disability intensity

The LR for definite or possible migraine diagnosis varies with the number of features present: with ≥4, 3 and ≥2 features, the LRs are 24 (1.5-388), 3.5 (1.3-9.2), and 0.41 (0.32-0.52), respectively.

Conclusion: Anti-convulsants are effective in reducing migraine frequency and reasonably well-tolerated. Valproate and topiramate are the two most studied but further studies of head-to-head comparisons between agents is needed.

Does this patient with headache need neuroimaging? In patients with new or changed headache the prevalence of significant intracranial pathology is 32% (24-42%), and in those presenting with thunderclap headache the prevalence is 43% (20-64%).

Several individual clinical features were found to be predictive of significant intracranial pathology:

Symptom
Cluster type headache
Abnormal neurological exam
Unilateral type headache
Headache with aura
Headache with vomiting

N/V
Polyphasia rheumatica
Visual loss
Headache with vomiting

Conclusion: New or changed headache requires neuroimaging. In patients presenting with thunderclap headache or headache with aura, neuroimaging is warranted.
Table 25. Headaches – Selected Serious but Rare Secondary Types (continued)

<table>
<thead>
<tr>
<th>Meningeal Irritation</th>
<th>Increased ICP</th>
<th>Temporal Arteritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Signs</td>
<td>Kernig’s sign</td>
<td>Focal neuro symptoms</td>
</tr>
<tr>
<td></td>
<td>Brudzinski’s sign</td>
<td>Papilledema</td>
</tr>
<tr>
<td></td>
<td>Meningismus</td>
<td></td>
</tr>
<tr>
<td>Management</td>
<td>CT/MRI with gadolinium</td>
<td>CT/MRI and treatment to reduce pressure</td>
</tr>
<tr>
<td></td>
<td>LP, antibiotics for bacterial meningitis</td>
<td>See Neurosurgery, NS7</td>
</tr>
<tr>
<td>Etiology</td>
<td>Meningitis, SAH</td>
<td>Tumour, IIH, malignant HTN</td>
</tr>
</tbody>
</table>

NI = diaphasic intracranial HTN

Migraine Headaches

Definition (Common Migraine)

• ≥5 attacks fulfilling each of the following criteria
  ▪ 4–72 h duration
  ▪ 2 of the following: unilateral, pulsating, moderate-severe (interferes with daily activity), aggravated by routine physical activity
  ▪ 1 of the following: nausea/vomiting, photophobia/phonophobia/osmophobia

Epidemiology

• 18% females, 6% males; frequency decreases with age (especially at menopause)

Etiology and Pathophysiology

• theories of migraine etiology
  ▪ depolarizing wave of “cortical spreading depression” across the cerebral cortex that may cause an aura (e.g. visual symptoms due to wave through occipital cortex) and also activate trigeminal nerve afferent fibres
  ▪ possible association with vasoconstriction/dilation
  ▪ significant genetic contribution

• triggers: stress, sleep excess/deprivation, drugs (estrogen, nitroglycerin), hormonal changes, caffeine withdrawal, chocolate, tyramines (e.g. red wine), nitrates (e.g. processed meats)

Signs and Symptoms

• stages of uncomplicated migraine
  i. prodrome (hours to days before headache onset)
  ii. aura
  iii. headache (see Table 23 for description of typical headache)
  iv. postdrome
  • aura
    ▪ fully reversible symptom of focal cerebral dysfunction lasting <60 min
    ▪ examples: visual disturbance (fortification spectra – zigzags; scintillating scotomata – spots), unilateral paresthesia and numbness or weakness, aphasia
  • prodrome/postdrome: appetite change, autonomic symptoms, altered mood, psychomotor agitation/retardation
  • classification of migraines
    ▪ common migraine: no aura
    ▪ classic migraine: with aura (headache follows reversible aura within 60 min)
    ▪ complicated migraine: with severe/persistent sensorimotor deficits
      ▪ examples
        – basilar-type migraine (occipital headache with diplopia, vertigo, ataxia, and altered level of consciousness)
        – hemiplegic/hemisensory migraine
        – ophthalmoplegic migraine
    ▪ acephalic migraine (i.e. migraine equivalent): aura without headache

Treatment

• avoid triggers
• mild to moderate migraine
  ▪ 1st line: NSAIDs (ibuprofen, naproxen)
  ▪ moderate to severe migraine
    ▪ triptans (most effective), ergots (dihydroergotamine, DHE)
    ▪ migraine prophylaxis: anticonvulsants (divalproex, topiramate, gabapentin), TCA (amitriptyline, nortriptyline), propranolol, calcium channel blocker (verapamil)

The oral contraceptive pill is contraindicated with complicated migraine due to risk of stroke

Migraine auras can mimic other causes of transient neurological deficits (e.g. TIA and seizures)

“If patient presents to ED with severe migraine and N/V – consider treating with IV anti-emetics (chlorpromazine, prochlorperazine)

“Menstrual Migraine” Subtype
Migraine headache that is associated with the onset of menstruation – usually 2 d before to 3 d after the onset of menstrual bleeding

Pharmacological Treatments for Acute Migraine

Pain 2002;97:247-257

Study: Meta-analysis of 54 double-blind, placebo-controlled RCTs of pharmacologic treatment of acute migraine of moderate to severe intensity (21,022 patients in total).

Data Extraction: Number of patients, dosing regimen, details of study design, timing or type of rescue medication. Outcomes include headache relief at 1 and 2 h, freedom from pain at 2 h, sustained relief for 24 h, and adverse effects within 24 h.

Main Results: Data were available for 9 oral medications, 2 intranasal medications, and subcutaneous sumatriptan. For H/A relief at 2 h, all interventions were effective except Celebrex®, with NNTs ranging from 2.0 for sumatriptan 6 mg SC to 5.4 for naratriptan 2.5 mg. The lowest NNT for oral medication was 2.6 for eletriptan 80 mg. For patients pain free at 2 h, the lowest NNT was 2.1 for sumatriptan 6 mg SC, with the lowest NNT for oral medication being 3.1 for rizatriptan 10 mg. For sustained relief over 24 h NNT ranged from 2.8 for eletriptan 80 mg to 8.3 for naratriptan 5 mg. Side effects could not be analyzed systematically. There were no drug-to-drug comparisons.

Conclusion: Overall, most treatments were effective. Subcutaneous sumatriptan and oral triptans were most effective.

A prophylactic agent is recommended only if migraine attacks are severe enough to cause impairment of a patient’s quality of life or if a patient has >3 migraines/mo that have not responded adequately to treatment

Neurology 2000;55:754-763
Sleep Disorders

Overview of Sleep

Definition
- newborn: 18 h sleep (50% REM), adolescents: 10 h, adults: 7-9 h but most get insufficient amounts
- many elderly have reduced sleep as a consequence of underlying sleep disorders

Sleep Architecture
- polysomnogram (PSG) measures: EEG, eye movements (electro-oculogram – EOG), EMG, respiratory effort, oxygenation, ECG

Table 26. Sleep Stage Characteristics

<table>
<thead>
<tr>
<th>EEG</th>
<th>EOG</th>
<th>Muscle Tone</th>
<th>Other Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Waking State</td>
<td>Alpha waves: high frequency (8-13 Hz), low voltage</td>
<td>Rapid, blinking</td>
<td>High</td>
</tr>
<tr>
<td>Stage N1 (~5%)</td>
<td>Alpha waves: high frequency (8-13 Hz), low voltage</td>
<td>Slow, roving eye movements</td>
<td>High, but gradually dropping Marker for very light quality sleep or sleep disruption</td>
</tr>
<tr>
<td>Stage N2 (~50%)</td>
<td>K complexes (high voltage negative and positive discharges) with sleep spindles (11-16 Hz)</td>
<td>Still</td>
<td>High</td>
</tr>
<tr>
<td>Stage N3 (previously 3 and 4)/Slow Wave/Delta Sleep (~20%)</td>
<td>Delta waves: low frequency (&lt;2 Hz), high voltage (&gt;75 µV)</td>
<td>Still</td>
<td>Low: Homeostatic sleep Reduced BP, HR, cardiac output, RR Growth hormone release</td>
</tr>
<tr>
<td>Rapid Eye Movement (REM) Sleep (~25%)</td>
<td>Sawtooth waves, mixed frequency, low voltage</td>
<td>Rapid eye movements</td>
<td>Very low: Irregular respiration Arrhythmias, heart rate variation Classical dreaming state</td>
</tr>
</tbody>
</table>

Disturbances of Alertness and Sleep

Coma
- see Neurosurgery, NS34

Insomnia
- definition/criteria
  - difficulty initiating or maintaining sleep, or waking up earlier than desired (leading to sleep that is chronically non-restorative/poor quality) despite adequate opportunity and circumstances for sleep
- types
  - sleep state misperception, psychophysiologic insomnia (learned sleep-preventing associations – i.e. clock watching), fatal familial insomnia (rare prion protein mutation causing autonomic dysfunction), idiopathic (lifelong difficulty)
- secondary causes
  - psychiatric disorders (80% of psychiatric patients): anxiety and depression (see Psychiatry, PS10)
  - neurologic disorders: neurodegenerative disease, epilepsy, neuromuscular disorders, many others
  - sleep disorders: restless legs syndrome (sleep initiation difficulties), sleep apnea (sleep maintenance difficulties)
  - medical conditions: pregnancy, cardiorespiratory (COPD/HF), GERD, pain (arthritis, fibromyalgia, cancer)
  - drugs/toxins: caffeine, alcohol, stimulants, antidepressants, glucocorticoids, sedative withdrawal
- treatment
  - sleep log, sleep hygiene, stimulus control, sleep restriction, relaxation response, CBT

Drug Effects on Wakefulness and Sleep
- Antihistamines associated with increased sleepiness
- Stimulants increase arousal
- Caffeine (an adenosine antagonist) increases wakefulness
- Benzodiazepines reduce slow wave sleep
- Antidepressants (TCA/MAOI/SSRI) reduce REM, prolong REM latency
- Alcohol may hasten sleep onset but associated with increased arousals
Sleep Apnea
- **definition**
  - disorder of breathing in sleep associated with sleep disruption and consequent excessive somnolence (or drowsiness)
- **epidemiology**
  - >2-4% of the population
  - increasing obesity
  - significant morbidity: HTN, stroke, heart failure, sleepiness, mortality (accidents)
- **types**
  - obstructive sleep apnea: see *Respirology*, R31
  - central sleep apnea: no effort to breathe over 10 s
  - mixed apnea: starts as central, but eventually becomes obstructive
- **etiology of central apnea:** heart failure, opiates, brainstem pathology, myotonic dystrophy
- **diagnosis:** apnea hypopnea index (AHI) or respiratory disturbance index (RDI) should be <5 in the normal state
- **treatment:** conservative measures, dental devices, CPAP (common), surgery (rare), ensure driving safety

Restless Leg Syndrome and Periodic Limb Movement in Sleep
- **definition**
  - urge to move accompanied by uncomfortable sensations that begin or worsen with rest, are partially or totally relieved with movement, and are worse in evening/night
  - RLS refers to sensation
  - PLMS refers to the manifestation
- **epidemiology:** 10% North Americans, 90% of RLS have PLMS, 50% of patients with PLMS have RLS
- **etiology:** central (spasticity), peripheral nervous system (radiculopathy, neuropathy), pregnancy, iron deficiency, alcohol use
- **treatment**
  - underlying contributors (iron and B12 supplementation), dopaminergic agonists (first line), clonazepam (causes tachyphylaxis), opioids (only exceptional circumstances)
  - NOT recommended: Sinemet®, causes augmentation

Narcolepsy
- **definition/clinical features:** excessive daytime sleepiness (all narcolepsy), cataplexy = loss of muscle tone with emotional stimuli (pathognomonic), sleep paralysis (unable to move upon wakening), hypnagogic hallucinations (vivid dreams or hallucinations at sleep onset)
- **epidemiology:** prevalence 1:2,000, onset in adolescence/early adulthood; life-long disorder
- **etiology:** presumed autoimmune attack on orexin/hypocretin system, post head injury, MS, hypothalamic tumours; rarely familial
- **diagnosis:** based on clinical history + multiple sleep latency test findings of short sleep latency <8 min and REM within 15 min of sleep onset on 2/4 naps
- **treatment**
  - sleep hygiene and scheduled brief naps, restricted driving
  - alerting agents: modafinil (non-amphetamine stimulant), stimulant (i.e. methylphenidate)
  - anticitaplectic: TCAs, SSRIs, sodium oxybate

Parasomnias
- **definition/clinical features:** unusual behaviours in sleep with clinical features appropriate to stage of sleep
- **etiology:** in elderly, REM sleep behaviour disorder may be associated with PD; in children, slow wave sleep arousals (sleep walking) may be associated with sleep disordered breathing
- **diagnosis:** clinical history in children, polysomnography in adults to exclude nocturnal seizures
- **treatment:** behavioural management (safety, adequate sleep); clonazepam for REM sleep behaviour, tonsillectomy if appropriate in children

Circadian Rhythm
- **definition/clinical features:** abnormalities based on time of day rather than sleep (i.e. jet lag, shift work)
- **diagnosis:** clinical history

CNS Infections
- see *Infectious Diseases*, ID18

Spinal Cord Syndromes
- see *Neurosurgery*, NS27
Stroke

Terminology

- **stroke**: sudden onset of neurological deficits of a vascular basis with infarction of CNS tissue
  - infarction is permanent tissue injury (confirmed by neuroimaging)
- **TIA**: sudden onset of neurological deficits of a vascular basis without infarction (i.e. no imaging evidence of stroke)

Pathophysiology

- two major types: ischemic (~80%) and hemorrhagic (~20%)

1. Ischemic
   - **arterial thrombosis**: thrombus formation in artery (local/in situ)
     - *large vessel*: stenosis or occlusion of the internal carotid artery, vertebral, or intracranial arteries
       - mechanisms
         - insufficient blood flow beyond lesion (hemodynamic stroke)
         - underlying processes: atherosclerosis (most common cause), dissection, and vasculitis
     - *small vessel/lacunar*
       - mechanism: chronic HTN and DM cause vessel wall thickening and decreased luminal diameter
       - affects mainly small penetrating arteries (primarily basal ganglia, internal capsule, and thalamus)
   - **cardioembolic**: blockage of cerebral arterial blood flow due to particles originating from a cardiac source
     - atrial fibrillation (most common), rheumatic valve disease, prosthetic heart valves, recent MI, fibrous and infectious endocarditis
   - **systemic hypoperfusion** (global cerebral ischemia)
     - inadequate blood flow to brain, usually secondary to cardiac pump failure (e.g. cardiac arrest, arrhythmia, or MI)
     - primarily affects watershed areas (between the major cerebral arterial territories)

2. Hemorrhagic
   - **intracerebral hemorrhage**
     - mechanisms
       - hypertensive (most common): rupture of small microaneurysms (Charcot-Bouchard aneurysms) causing intraparenchymal hemorrhage
         - most common sites: putamen, thalamus, cerebellum, and pons
       - other: trauma, amyloid angiopathy (associated with lobar hemorrhage), vascular malformations, vasculitis, drug use (cocaine or amphetamines)
   - **subarachnoid hemorrhage** see Neurosurgery, NS18

Stroke Syndromes According to Vascular Territory

- **ACA**: contralateral leg paresis, sensory loss, cognitive deficits (e.g. apathy, confusion, and poor judgment)
- **MCA**: proximal occlusion involves
  1. contralateral weakness and sensory loss of face and arm
  2. cortical sensory loss
  3. may have contralateral homonymous hemianopia or quadrantanaopia
  4. if dominant (usually left) hemisphere: aphasia
  5. if non-dominant (usually right) hemisphere: neglect
  6. eye deviation towards the side of the lesion and away from the weak side
- **PCA**
  1. contralateral hemianopia or quadrantanaopia
  2. midbrain findings: CN III and IV palsy/pupillary changes, hemiparesis
  3. thalamic findings: sensory loss, amnesia, decreased level of consciousness
  4. if bilateral: cortical blindness or prosopagnosia
- **basilar artery** (locked-in syndrome):
  1. quadriparesis
  2. dysarthria
  3. impaired eye movements
- **PICA** (lateral medullary or Wallenberg syndrome): ipsilateral ataxia, ipsilateral Horner’s, ipsilateral facial sensory loss, contralateral limb impairment of pain and temperature sensation, nystagmus, vertigo, nausea/vomiting, dysphagia, dysarthria, hicups

Hypertension Encephalopathy

Acute severe HTN (typically dBP >130 or sBP >200) can cause hypertensive encephalopathy – abnormal fundoscopic exam (papilledema, hemorrhages, exudates, cotton-wool spots), focal neurologic symptoms, N/V, visual disturbances, and change in LOC

Consider transfer of acute stroke patient to a designated stroke centre for neuroprotective or thrombolytic therapy if the patient is seen in first few hours

Early seizure activity occurs in 5-25% of patients after ICH

Cerebral venous sinus thrombosis should be considered in the differential diagnosis of stroke and headache. It is an uncommon cause of either, but is associated with high morbidity and mortality. Patients often present with headache alone, but can also have seizures, focal neurological deficits, or cranial nerve palsies. This is diagnosed with MRV or CTV. Treatment is typically anticoagulation with heparin initially, then transition to warfarin

20-40% of patients with ischemic stroke may develop hemorrhagic transformation within 1 wk after the initial infarction

Blood work should only delay treatment if: patient is on anticoagulants, low platelet count suspected, abnormal electrolytes suspected, or any bleeding abnormality suspected

Suspect an alternate diagnosis if: fever, decreased LOC, fluctuating symptoms, gradual onset, no focal neurological symptoms, and/or positive symptoms

Infarcted area of brain tissue can often appear normal on CT during the first several hours after the onset of stroke
- **medial medullary infarct** (anterior spinal artery, which can be associated with anterior cord infarct): contralateral hemiparesis (facial sparing), contralateral impaired proprioception and vibration sensation, ipsilateral tongue weakness

- **lacunar infarcts (deep hemispheric white matter)**
  - pure motor hemiparesis (posterior limb of internal capsule): contralateral arm, leg, and face
  - pure sensory loss (thalamic): hemisensory loss
  - ataxic hemiparesis: ipsilateral ataxia and leg paresis
  - dysarthria-clumsy hand syndrome: dysarthria, facial weakness, dysphagia, mild hand weakness and clumsiness

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**Assessment and Treatment of Ischemic Stroke**

**General Assessment**
- ABCs, full vital sign monitoring, capillary glucose, (Accu-Chek®), urgent CODE STROKE if <4.5 h from symptom onset (for possible thrombolysis)
- level of consciousness (knows age, month, obeys commands), dysarthria, anomia (cannot name objects), gaze preference, visual fields, facial palsy
- arm drift, leg weakness, ataxia
- sensation to pinprick, extinction/neglect
- history
  - onset: time when last known to be awake and symptom free
  - mimics to rule out: seizure/post-ictal, hypoglycemia, migraine, conversion disorder
- investigations
  - non-contrast CT head (STAT): to rule out hemorrhage and assess extent of infarct
  - ECG: to rule out atrial fibrillation (cardioembolic cause)
  - CBC, electrolytes, creatinine, PTT/INR, blood glucose
- imaging (i.e. CT) signs of stroke
  - loss of cortical white-grey differentiation
  - sulcal effacement (i.e. mass effect decreases visualization of sulci)
  - hypodensity of parenchyma
  - insular ribbon sign
  - hyperdense MCA sign

**Aspect Score:** 10-point quantitative score to assess ischemic changes on CT scan
- 10/10 is normal and <4/10 signifies high risk of bleed with rtPA
- Subtract 1 point for each of following structures if abnormal within the ischemic hemisphere: caudate, lentiform, insula, internal capsule, MCA 1, 2, 3, 4, 5, 6 regions

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The National Institute of Health Stroke Scale (NIHSS) is a standardized clinical examination that determines the severity of an acute stroke; it can also be used to monitor response to treatment over time. The scale uses 11 items that evaluate:
- Level of consciousness
- Visual system
- Motor system
- Sensory system
- Language abilities

Scoring (x/42):
- 0 = no stroke
- 1-4 = mild stroke
- 5-15 = moderate stroke
- 15-20 = moderate to severe stroke
- 21-42 = severe stroke

rtPA is typically considered if score ≥6, but some stroke neurologists will administer rtPA with lower NIH stroke scale scores
ACUTE STROKE MANAGEMENT

1. Thrombolysis
   • rtPA (recombinant tissue plasminogen activator)
   • given within 4.5 h of acute ischemic stroke onset provided there are clinical indications and no contraindications to use:
     • indications: based on NIH Stroke Scale (NIHSS – see sidebar)
     • contraindications: see sidebar

2. Anti-Platelet Therapy
   • give at presentation of TIA or stroke if rtPA not received
   • antplatelet agents
     • ASA: recommended dose 81 mg chewed
       • if patient intolerant to ASA, use other antiplatelet agent (i.e. clopidogrel)

3. Acute Anti-Coagulant Therapy
   • for patients with TIA or stroke and atrial fibrillation if rtPA not received
     • recommend IV heparin (or ensuring INR between 2-3 if already anticoagulated on warfarin)

4. Intra-arterial Thrombectomy by Interventional Radiology

Other Acute Management Issues
   • avoid hyperglycemia which can increase the infarct size
   • lower temperature if febrile (febrile stroke: think septic emboli from endocarditis)
   • avoid hyperglycemia which can increase the infarct size

Blood Pressure Control
   • do NOT lower the blood pressure unless the HTN is severe
     • antihypertensive therapy is withheld for at least 5 d after thromboembolic stroke unless
       sBP >220 mmHg or dBP >120 mmHg, or in the setting of acute MI, renal failure, aortic dissection
     • acutely elevated BP is necessary to maintain brain perfusion to the ischemic penumbra
     • most patients with an acute cerebral infarct are initially hypertensive and their BP will fall spontaneously within 1-2 d
     • IV labetalol first-line if needed

Etiological Diagnosis
   • further investigations
     • additional neuroimaging (MRI)
     • vascular imaging: CTA/MRA/carotid dopplers
     • cardiac tests: echocardiogram, Holter monitoring
     • correct etiological diagnosis is critical for appropriate secondary prevention strategies

Primary and Secondary Prevention of Ischemic Stroke

Anti-Platelet Therapy
   • primary prevention
     • current evidence has not firmly established a protective role for antiplatelet agents for
       low-risk patients without a prior stroke/TIA
   • secondary prevention
     • ASA is the initial antiplatelet of choice for stroke prevention
     • other agents (generally reserved for those who suffer cerebrovascular symptoms while on ASA
       or if unable to tolerate ASA)
       • Aggrenox® (ESPRIT trial)
       • clopidogrel (CAPRIE trial)

Carotid Stenosis
   • primary prevention (asymptomatic)
     • carotid endarterectomy is controversial: if stenosis >60%, risk of stroke is 2% per yr; carotid endarterectomy reduces the risk of stroke by 1% per yr (but 5% risk of complications)
   • secondary prevention (previous stroke/TIA in carotid territory)
     • carotid endarterectomy clearly benefits those with symptomatic severe stenosis (70-99%),
       and is less beneficial for those with symptomatic moderate stenosis (50-69%) (NASCET
       trial), see Vascular Surgery: VS8
according to the CREST trial, endarterectomy and carotid stenting have similar benefits in a composite endpoint of reduction of stroke, MI, and death; however, in the periprocedural period, stenting results in a higher rate of stroke, while endarterectomy results in a higher rate of MI.

**Atrial Fibrillation**
- primary and secondary prevention with antiocoagulation
  - classically risk stratification used CHADS² score, but Stroke 2014 guidelines recommend that virtually all patients with atrial fibrillation without contraindication be antiocoagulated
    - 0 (very low risk): antiplatelet
    - 1 (low risk): antiocoagulant or antiplatelet – patient specific decision
    - >2 (mod-high risk): antiocoagulant
  - antiocoagulation therapy
    - warfarin (titrate to INR 2-3)
    - dabigatran (110 or 150 mg PO bid), apixaban (2.5 or 5 mg PO bid) or rivaroxaban (15 or 20 mg PO daily) may be alternatives to warfarin, but should be used cautiously due to lack of a reversal agent should bleeding occur

**Hypertension**
- primary prevention
  - targets: BP <140/90 (or <130/80 for diabetics or renal disease)
  - ramipril 10 mg PO OD is effective in patients at high risk for cardiovascular disease (HOPE trial)
  - ACEI reduce the risk of stroke beyond their antihypertensive effect
- secondary prevention
  - ACEI and thiazide diuretics are recommended in patients with previous stroke/TIA (PROGRESS trial)

**Hypercholesterolemia**
- primary prevention
  - statins reduce the risk of stroke in patients with CAD or at high risk for cardiovascular events, even with normal cholesterol (CARE trial)
- secondary prevention
  - statins reduce risk of subsequent stroke – best evidence is for high dose atorvastatin (SPARCL trial) but lower doses may be more appropriate if patient cannot tolerate high dose

**Diabetes**
- ideal management: HbA1c <7%, fasting blood glucose between 4 and 7

**Smoking**
- primary prevention
  - smoking increases risk of stroke in a dose-dependent manner
- secondary prevention
  - after smoking cessation, the risk of stroke decreases to baseline within 2-5 yr

**Physical Activity**
- regular physical activity is an important lifestyle measure in stroke prevention and its beneficial effect has a dose-related response in terms of intensity and duration of activity

**Stroke Rehabilitation**
- individualized based on severity and nature of impairment; may require inpatient program and continuation through home care or outpatient services
- multidisciplinary approach includes dysphagia assessment and dietary modifications, communication rehabilitation, cognitive and psychological assessments including screen for depression, therapeutic exercise programs, assessment of ambulation and evaluation of need for assistive devices, splints or braces, vocational rehabilitation

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**Cerebral Hemorrhage**

**Investigations**
- general investigations, see *Assessment and Treatment of Ischemic Stroke*, N51
- further investigations
  - LP (if suspect subarachnoid hemorrhage despite negative CT)
  - may require cerebral angiogram if suspect aneurysm or AVM
  - if typical location for hypertensive hemorrhage, repeat CT head in 4-6 wk after hemorrhage has resolved to rule out an underlying lesion
Treatment
• medical
  • anti-hypertensives: no conclusive BP target ranges for managing ICH exist; 2010 AHA/ASA
guidelines suggest that reducing sBP to as low as 140 mmHg with IV anti-hypertensives is
safe and appropriate management (target sBP 140-160 systolic)
  • ICP lowering medical management (if necessary): see Neurosurgery, NS7
• surgical: see Neurosurgery, NS20

Neurocutaneous Syndromes
• see Pediatrics, P86

Multiple Sclerosis
Definition
• a chronic inflammatory disease of the CNS characterized by relapsing remitting, or progressive
  neurologic symptoms due to inflammation, demyelination, and axonal degeneration

Clinical Patterns of MS
• relapsing remitting (RRMS) 85%, primary progressive (PPMS) 10%, progressive relapsing
  (PRMS) 5%, secondary progressive (SPMS)
• benign MS (BMS): retrospective diagnosis made after 15 years of mild disease, with no evidence
  of worsening (in functional ability and MRI)
• most RRMS goes on to become SPMS

MS Variants
• Devic’s = neuromyelitis optica (NMO): severe optic neuritis and extensive transverse myelitis
  extending >3 vertebral segments (NMO antibody positive)
• clinically isolated syndrome (CIS): single MS-like episode, which may progress to MS
• tumefactive MS: solitary lesion >2 cm mimicking neoplasms on MRI
• fulminant MS (Marburg): rapidly progressive and fatal MS associated with severe axonal
damage, inflammation, and necrosis
• pediatric MS: onset of MS before the age of 18
  • epidemiology: rare (1.35-2.5 per 100,000 children)
  • presentation: more likely to present with isolated optic neuritis, isolated brainstem syndrome
    or symptoms of encephalopathy compared to adults
  • course: 98% have RRMS
  • diagnosis and treatment similar to adult MS
• differential diagnosis: in the setting of nonspecific CSF abnormalities and MRI evidence of
  white matter lesion, rule out ADEM, optic neuritis, transverse myelitis, neuromyelitis optica,
  CNS malignancies, leukodystrophies, and mitochondrial disease
• acute disseminated encephalomyelitis (ADEM): monophasic demyelinating disorder with
  multifocal neurologic symptoms seen mainly in children often following infection or vaccination

Etiology
• genetic
  • polygenetic: the HLA-DRB1 gene has been demonstrated to be a genetically susceptible area
  • 30% concordance for monozygotic twins, 2-4% risk in offspring of affected mother or father
• environmental
  • MS is more common in regions with less sun exposure and lower stores of vitamin D
    (Europe, Canada, US, New Zealand, SE Australia)
  • MS has also been linked to certain viruses (EBV is associated with MS)

Epidemiology
• onset 17-35 yr; F:M = 3:1
• PPMS occurs in an older population with F=M

Diagnosis
• dissemination in space and in time as based on the revised McDonald criteria
  • dissemination in space: clinical evidence of 2 or more lesions, or three of
    (1 gadolinium enhancing or 9 T2 lesions), (1 infratentorial lesion), (1 juxtacortical lesion),
    (3 periventricular lesions)
Clinical Features
- symptoms include numbness, visual disturbance (optic neuritis), weakness, spasticity, diplopia (e.g. INO), impaired gait, vertigo, bladder dysfunction
- **Lhermitte's sign**: flexion of neck causes electric shock sensation down back into limbs indicating cervical cord lesion
- **Uthoff’s phenomenon**: worsening of symptoms (classically optic neuritis) in heat
- SPMS: classically weakness of legs in pyramidal distribution paired with cerebellar findings of arms (i.e. intention tremor)
- symptoms not commonly found in MS: visual findings of new onset, visual field defects, aphasia, apraxia, progressive hemiparesis
- relapse: acute/subacute onset of clinical dysfunction that peaks from days to weeks, followed by remission with variable symptom resolution (symptoms must last at least 24 h)
- in RRMS, average 0.4 to 0.6 relapses/yr, but higher disease activity in 1st yr of disease

Investigations
- MRI: demyelinating plaques appear as hyperintense lesions on T2 weighted MRI, with active lesions showing enhancement with gadolinium
  - typical locations: periventricular, corpus callosum, cerebellar peduncles, brainstem, juxtacortical region, and dorsolateral spinal cord
  - Dawson's fingers: periventricular lesions extending into corpus callosum
  - cranial MRI is more sensitive than spinal MRI
- **CSF**: oligoclonal bands in 90%, increased IgG concentration
- **evoked potentials (visual/auditory/somatosensory)**: delayed but well-preserved wave forms

Treatment
- **acute treatment**: methylprednisolone 1,000 mg IV daily x 3-7 d (no taper required); if poor response to corticosteroids may consider plasma exchange
- disease modifying therapy (DMT)
  - goals: decrease relapse rate, decrease progression of disability, slow accumulation of MRI lesions
  - first line: interferon-β (injection: Betaseron®, Avonex®, Rebif®), glatiramer acetate (injection: Copaxone®)
  - second line: natalizumab (Tysabri®) (monthly IV infusion)
  - new oral agents: fingolimod (Gilenya®)
  - indications for fingolimod: newly diagnosed patients with active RRMS who prefer oral treatment despite increased risks or those intolerant of first line therapies
  - CIS: early treatment with interferons may delay potential second attack
  - RRMS: DMT reduces rate of relapse by about 30%
  - PPMS/SPMS: no proven efficacy of DMTs
- symptomatic treatment
  - spasticity: baclofen, tizanidine, dantrolene, benzodiazepine, botulinum toxin
  - bladder dysfunction: oxybutynin
  - pain: TCA, carbamazepine, gabapentin
  - fatigue: amantadine, modafinil, methylphenidate
  - depression: antidepressant, lithium
  - constipation: high fibre intake, stool softener, laxatives
  - sexual dysfunction: sildenafil (Viagra®), tadalafil (Cialis®), vardenafil (Levitra®, Staxyn®)
- **education and counseling**: MS Society, support groups, psychosocial issues

Prognosis
- good prognostic indicators: female, young, RRMS, presenting with optic neuritis, low burden of disease on initial MRI, low rate of relapse early in disease
- PPMS: poor prognosis, higher rates of disability, poor response to therapy

**Chronic Cerebrospinal Venous Insufficiency (CCSVI)**
A theory proposed in 2008 describing abnormal venous blood flow in patients with MS; while some RCTs are still underway, recent studies have largely discredited this highly controversial theory. That is, studies indicate no connection between CCSVI and MS

**The Expanded Disability Status Scale (EDSS)**
Is used as a measure of disability progression and is scored from 0 to 10 based on the neurologic exam and ambulation

**Oral Fingolimod or Intramuscular Interferon for Relapsing Multiple Sclerosis**
*NEJM* 2010;362:402-415
Method: Multicentre double-blind RCT.
Population: 1,292 patients with relapsing-remitting MS and at least one relapse.
**Intervention**: Oral fingolimod at 0.5–1.25 mg or 30–120 IM interferon (IFN-
**Outcomes**: Annualized relapse rate over 1 yr; lesions on T2-weighted MRI.
**Results**: Annualized relapse rate was lower in both groups receiving fingolimod compared to interferon: 0.30 (95% CI 0.19–0.26) with 1.25 mg fingolimod, 0.18 (95% CI 0.12–0.21) with 0.5 mg fingolimod, 0.33 with interferon (95% CI 0.26–0.42; p < 0.001). MRI findings also showed greater reduction of lesions in fingolimod-treated patients. Progression of disability was unchanged. Side effects included severe infections like HSV encephalitis, disseminated VZV, other HSV infections, and skin cancer.
**Conclusions**: Oral fingolimod is superior to interferon-β injections in reducing relapses and MRI lesion load in patients with MS.

**Recombinant Interferon Beta or Glatiramer Acetate for Delaying Conversion of the First Demyelinating Event to Multiple Sclerosis**
*Cochrane DB Syst Rev* 2008;2:CD005278
Study: Meta-analysis of RCTs of clinically isolated syndrome (CIS) patients treated with immunomodulatory drugs.
**Primary Outcome**: Proportion of patients converting to clinically definite MS and adverse effects.
**Results**: Three trials (n = 1,160) tested the efficacy of interferon (IFN-β) and no trial tested glatiramer acetate (GA). A pooled odds ratio (OR) of 0.53 (95% CI 0.40–0.71; p < 0.001) for patients on IFN vs. placebo at 1 yr. Two year follow-up odds ratio was 0.52 (95% CI 0.38–0.70; p < 0.001). There was no significant increase in adverse events for those on IFN-β.
**Conclusions**: IFN-β treatment can delay progression to clinically definite MS in patients with CIS over 2 yr.
<table>
<thead>
<tr>
<th>Indications</th>
<th>Mechanism of Action/Class</th>
<th>Generic Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Contraindications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson’s Disease</td>
<td>Dopamine precursor</td>
<td>levodopa + carbidopa</td>
<td>Sinemet®</td>
<td>Carbidopa 25 mg/levodopa 100 mg PO tid Maximum 200 mg carbidopa and 2,000 mg levodopa per day</td>
<td>Narrow-angle glaucoma, use of MAO inhibitor in last 14 d, history of melanoma or undiagnosed skin lesions</td>
<td>Nausea, hypotension, hallucinations, dyskinesias in last 14 d, history of melanoma or undiagnosed skin lesions</td>
</tr>
<tr>
<td></td>
<td>Dopamine agonist</td>
<td>bromocriptine</td>
<td>Parodel®</td>
<td>1.25 mg PO bid, increase by 2.5 mg/d q2-4wk, up to 10-30 mg PO tid</td>
<td>Concomitant use of potent inhibitors of CYP3A4, uncontrolled HTN, ischemic heart disease, peripheral vascular disease; caution with renal or hepatic disease</td>
<td>Hypotension, N/V, diziness, constipation, diaphoresis, muscle cramps, H/A, nasal congestion, drowsiness, hallucinations</td>
</tr>
<tr>
<td></td>
<td>MAO B inhibitor</td>
<td>selegline</td>
<td>Eldepryl®</td>
<td>5 mg PO bid</td>
<td>Concomitant use of meperidine or tricyclic antidepressants</td>
<td>H/A, insomnia, diziness, nausea, dry mouth, hallucinations, confusion, orthostatic hypotension, increased akinesia, risk of hypertensive crisis with tyramine-containing foods</td>
</tr>
<tr>
<td>Myasthenia Gravis</td>
<td>Acetylcholinesterase inhibitor</td>
<td>pyridostigmine</td>
<td>Mestinon®</td>
<td>600 mg/d PO divided in 5-6 doses Range 60-1,500 mg/d</td>
<td>GI or GU obstruction</td>
<td>Nausea, vomiting, diaphoresis, abdominal cramps, increased peristalsis, increased salivation, increased bronchial secretions, miosis, diaphoresis, muscle cramps, fasciculations, muscle weakness</td>
</tr>
<tr>
<td>Acute Migraine</td>
<td>Triptan (selective 5-hydroxytryptamine receptor agonist)</td>
<td>sumatriptan</td>
<td>Imitrex®</td>
<td>25-100 mg PO pm, maximum 200 mg/d</td>
<td>Hemiplegic/basilar migraine, ischemic heart disease, CVD, uncontrolled HTN, ischemic heart disease, peripheral vascular disease; caution with renal or hepatic disease</td>
<td>Vertigo, chest pain, flushing, sensation of heat, hypertensive crisis, peripheral vascular disease, coronary artery vasospasm, cardiac arrest, nausea, vomiting, H/A, hyposalivation, fatigue</td>
</tr>
<tr>
<td></td>
<td>Ergot (5-HT1D receptor agonist)</td>
<td>dihydroergotamine</td>
<td>Migranal®</td>
<td>Nasal spray 0.5 mg/spray, maximum 4 sprays/d</td>
<td>Hemiplegic/basilar migraine, high-dose ASA therapy, uncontrolled HTN, ischemic heart disease, peripheral vascular disease, severe hepatic or renal dysfunction; use of triptans in last 24 h, use of MAO inhibitors in last 14 d</td>
<td>Coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, ventricular fibrillation; may cause significant rebound H/A</td>
</tr>
<tr>
<td>Migraine Prophylaxis</td>
<td>Anticonvulsant</td>
<td>topiramate</td>
<td>Topamax®*</td>
<td>25 mg OD PO (in evening); may increase weekly by 25 mg/d to a max 50 mg bid</td>
<td>Uncompensated CHF, severe bradycardia or heart block, severe COPD or asthma</td>
<td>Sedation, mood disturbance, cognitive dysfunction, anorexia, nausea, diaphoresis, paresthesias, metabolic acidosis, glaucoma, SJS/TEN</td>
</tr>
<tr>
<td></td>
<td>β-blocker</td>
<td>propranolol</td>
<td>Inderal®*</td>
<td>80 mg/d divided every 6-8 h; increase by 20-40 mg/dose every 3-4 wk to max 160-240 mg/d in divided doses q8-8h</td>
<td>Hypotension, SJS/TEN, SLE-type symptoms, CNS depression, blood dyscrasias, nystagmus, N/V, constipation, sedation, teratogenic</td>
<td>Fatigue, cognitive dysfunction, disturbed sleep, rashes, dyspepsia, dry eyes, heart failure, bronchospasm, risk of acute tachycardia and HTN if withdrawal</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>Anticonvulsant for partial ± 2° generalization, generalized tonic-clonic</td>
<td>carbamazepine</td>
<td>Tegretol®</td>
<td>Start at 100-200 mg PO OD-tid, increase by 200 mg/d up to 800-1,200 mg/d</td>
<td>History of bone marrow depression, hepatic disease, hypersensitivity to the drug, use of MAO inhibitor in last 14 d</td>
<td>Drowsiness, H/A, unsteadiness, diziness, N/V, skin rash, agranulocytosis/aplastic anemia (rare)</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant for partial, tonic-clonic, status epilepticus</td>
<td>phenytoin</td>
<td>Dilantin®</td>
<td>100 mg PO tid, maintenance dose up to 200 mg PO tid SE: 10-15 mg/kg IV loading dose then maintenance doses of 150 mg PO or IV q8-8h</td>
<td>Hypersensitivity, pregnancy, breastfeeding; caution with P-450 interactions</td>
<td>Hypotension, SJS/TEN, SLE-type symptoms, gingival hypertrophy, peripheral neuropathy, H/A, blood dyscrasias, nystagmus, N/V, constipation, sedation, teratogenic</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant for partial or generalized, absence seizures</td>
<td>valproic acid</td>
<td>Depakene®</td>
<td>10-15 mg/kg/d PO in divided doses, increase incrementally until therapeutic dose to max of 60 mg/kg/d</td>
<td>Hypersensitivity, hepatic disease, urea cycle disorders</td>
<td>Hepatic failure, H/A, somnolence, alopecia, N/V, diaphoresis, diplopia, thrombocytopenia, hypothermia, pancreatitis, encephalopathy</td>
</tr>
<tr>
<td></td>
<td>Anticonvulsant for absence seizures</td>
<td>ethosuximide</td>
<td>Zarontin®</td>
<td>500 mg/d PO, increase by 250 mg every 4-7 d to max 1.5 g/d in divided doses</td>
<td>Hypersensitivity (succinimides)</td>
<td>CNS depression, blood dyscrasias, SLE, SJS, GI symptoms</td>
</tr>
<tr>
<td>Table 27. Common Medications – Major Issues (continued)</td>
<td></td>
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<tr>
<td>------------------------------------------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td><strong>Mechanism of Action/Class</strong></td>
<td><strong>Generic Name</strong></td>
<td><strong>Trade Name</strong></td>
<td><strong>Dosing</strong></td>
<td><strong>Contraindications</strong></td>
<td><strong>Side Effects</strong></td>
</tr>
<tr>
<td>------------------------------------------------------</td>
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<td>--------------------------------------------------------------------------------------</td>
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</tr>
<tr>
<td>Stroke Prevention in AF</td>
<td>Anticoagulant (direct thrombin inhibitor)</td>
<td>dabigatran</td>
<td>Pradaxa®</td>
<td>110 mg PO bid or 150 mg PO bid</td>
<td>CrCl &lt; 30 mL/min, significant hemostatic impairment or CNS lesions within 6 mo with high risk of bleeding</td>
<td>Dyspepsia, gastritis, bleeding</td>
</tr>
<tr>
<td></td>
<td>Anticoagulant (Factor Xa inhibitor)</td>
<td>rivaroxaban</td>
<td>Xarelto®</td>
<td>15 mg PO daily or 20 mg PO daily</td>
<td>Concomitant anticoagulant, hepatic disease, pregnancy, strong CYP3A4 and P-gp inhibitors e.g. itraconazole, ritonavir</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>Anticoagulant (Factor Xa inhibitor)</td>
<td>apixaban</td>
<td>Eliquis®</td>
<td>2.5 mg PO bid or 5 mg PO bid</td>
<td>Active bleeding, gastrointestinal bleeding, recent cerebral infarction, active peptic ulcer disease with recent bleeding, hepatic disease with coagulopathy</td>
<td>Bleeding (conjunctival, gastrointestinal, gingival, contusion, hematomata, epistaxis, hematuria)</td>
</tr>
<tr>
<td>Mild to Moderate AD or DLB</td>
<td>Cholinesterase Inhibitor</td>
<td>donepezil</td>
<td>Aricept®</td>
<td>5 mg PO OD, may increase to 10 mg PO OD after 4-6 wk</td>
<td>Hypersensitivity to donepezil or to piperidine derivatives</td>
<td>Diarrhea, N/V, insomnia, muscle cramps, fatigue, anorexia, HTN, syncope, AV block</td>
</tr>
<tr>
<td>Multiple Sclerosis MS Disease Modifying Therapy</td>
<td>interferon-β-1b</td>
<td>Betaseron®</td>
<td>0.25 mg (8 MU) SC every other day</td>
<td>Pregnancy, hypersensitivity to natural or recombinant interferon-β</td>
<td>Injection site reactions, injection site necrosis, flu-like symptoms (fever, chills, myalgia; tend to decrease over time)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>interferon-β-1a SC</td>
<td>Reband®</td>
<td>44 μg SC 3 times/wk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>interferon-β-1a IM</td>
<td>Avanex®</td>
<td>30 μg IM once weekly</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis MS Disease Modifying Therapy</td>
<td>glatiramer acetate</td>
<td>Copaxone®</td>
<td>20 mg SC OD</td>
<td>Hypersensitivity to glatiramer or mannitol</td>
<td>Injection site reactions, nausea, transient chest pain, vasodilation</td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis MS Disease Modifying Therapy</td>
<td>natalizumab</td>
<td>Tysabri®</td>
<td>300 mg IV given over 1 h, every 4 wk</td>
<td>Hypersensitivity to natalizumab, progressive multifocal leukoencephalopathy (PML)</td>
<td>Rash, nausea, arthralgia, H/A, infections, rare risk of PML and melanoma</td>
<td></td>
</tr>
<tr>
<td>Multiple Sclerosis MS Disease Modifying Therapy</td>
<td>fingolimod</td>
<td>Gilenya®</td>
<td>0.5 mg PO OD</td>
<td>Not available</td>
<td>Diarrhea, transaminits, H/A, bradyarrhythmia, lymphopenia</td>
<td></td>
</tr>
<tr>
<td>Spasticity (i.e. MS) Muscle Relaxant – Antispastic</td>
<td>baclofen</td>
<td>Lioresal®</td>
<td>5 mg PO tid, increase by 15 mg/d q3d to max dose 80 mg/d in three divided doses</td>
<td>Hypersensitivity to baclofen</td>
<td>Transient drowsiness, daytime sedation, dizziness, weakness, fatigue, convulsions, constipation, nausea</td>
<td></td>
</tr>
</tbody>
</table>
# Landmark Neurology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASCET</td>
<td><em>NEJM</em> 1991;7:445-53</td>
<td>Patients with symptomatic carotid stenosis of 70-99% benefited more from carotid endarterectomy than best medical therapy</td>
</tr>
<tr>
<td>Interferon-α Multiple Sclerosis Study Group Trial</td>
<td>Neurology 1993;43:655-61</td>
<td>Interferon-α-1b reduces relapse rate and severity of relapses in RRMS</td>
</tr>
<tr>
<td>NINDS rtPA</td>
<td><em>NEJM</em> 1995;333:1581-7</td>
<td>rtPA reduces mortality and long-term disability when administered within 3 h of acute stroke</td>
</tr>
<tr>
<td>SPARCL</td>
<td><em>NEJM</em> 2006;355:549-59</td>
<td>The observed benefit of statins in cardiovascular disease is also extended to patients with a recent stroke or TIA</td>
</tr>
<tr>
<td>ECASS 3</td>
<td><em>NEJM</em> 2008;359:1317-29</td>
<td>rtPA improved clinical outcomes when administered within 3 to 4.5 h of acute ischemic stroke</td>
</tr>
<tr>
<td>PROFESS</td>
<td><em>NEJM</em> 2008;359:1238-51</td>
<td>ASA + dipyridamole and clopidogrel showed similar benefits in secondary stroke prevention</td>
</tr>
<tr>
<td>RELY</td>
<td><em>NEJM</em> 2009;361:1139</td>
<td>Dabigatran superior to warfarin for stroke prevention in patients with atrial fibrillation</td>
</tr>
<tr>
<td>CREST</td>
<td><em>NEJM</em> 2010;363:11-23</td>
<td>Carotid stenting and endarterectomy had similar benefits in reduction of stroke, MI, and death in carotid stenosis, but in the periprocedural period, stenting had a higher rate of stroke, while endarterectomy had a higher rate of MI</td>
</tr>
<tr>
<td>INTERACT2</td>
<td><em>NEJM</em> 2013;368:2355-65</td>
<td>Intensive lowering of blood pressure (sBP &lt;140) in spontaneous intracerebral hemorrhage did not improve mortality or severe disability but improved functional outcomes (odds ratio for greater disability, 0.87; 95% CI, 0.77 to 1.00; P=0.04)</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td><em>NEJM</em> 2015;372:11-20</td>
<td>Intra-arterial treatment (intra-arterial thrombolysis, mechanical treatment, or both) for emergency revascularization administered within 6 h after stroke onset was effective and safe for acute ischemic stroke caused by proximal intracranial occlusion of the anterior circulation</td>
</tr>
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Acronyms

AVF arteriovenous fistula
AVM arteriovenous malformation
CBF cerebral blood flow
CSF cerebrospinal fluid
CPA cerebellar pontine angle
CPP cerebral perfusion pressure
CVR cerebrovascular resistance
DOBS deep brain stimulation
DIF diabetes insipidus
ECF extracellular fluid
ECT electroconvulsive therapy
EEG electroencephalography
EMG electromyography
EVD external ventricular drain
GCS Glasgow coma scale
GPI globus pallidus pars interna
H/A headache
IC internal capsule
ICF intracellular fluid
ICH intracerebral hemorrhage
ICP intracranial pressure
IVH intraventricular hemorrhage
LOC loss of consciousness
LP lumbar puncture
MAP mean arterial pressure
NPH normal pressure hydrocephalus
OPLL ossification of posterior longitudinal ligament
PAG peri-aqueductal grey matter
PET positron emission tomography
PLL posterior longitudinal ligament
PNET primitive neuroectodermal tumour
PVS periventricular grey matter
SAH subarachnoid hemorrhage
SDH subdural hemorrhage
SIADH syndrome of inappropriate antidiuretic hormone
SPECT single photon emission computed tomography
STN subthalamic nucleus
UMN upper motor neuron
VPL ventral posterolateral
VPM ventral posteromedial
WBRT whole brain radiation therapy

Basic Anatomy Review

MRI Brain

A. Sagittal Section

B. Axial Section

Figure 1. Magnetic resonance imaging (MRI) neuroanatomy

Figure 2. Relationship of nerve roots to vertebral level in the cervical and lumbar spine
Note: AP views depict left-sided C4-5 and L4-5 disc herniation, and correlating nerve root impingement
### Differential Diagnoses of Common Neurosurgical Presentations

<table>
<thead>
<tr>
<th>Intracranial Mass Lesions</th>
<th>Disorders of the Spine</th>
<th>Peripheral Nerve Lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>Extracranial</td>
<td>Neuropathies</td>
</tr>
<tr>
<td>Metastasis</td>
<td>Degenerative: disc herniation, canal stenosis, spondylothesis/spondyloysis</td>
<td>Traumatic</td>
</tr>
<tr>
<td>Astrocytoma</td>
<td>Infection/inflammation: osteomyelitis, discitis</td>
<td>Entrapments</td>
</tr>
<tr>
<td>Meningioma</td>
<td>Ligamentous: ossification of posterior longitudinal ligament (PLL)</td>
<td>Iatrogenic</td>
</tr>
<tr>
<td>Vestibular schwannoma (acoustic neuroma)</td>
<td>Trauma: mechanical compression/instability, hematomas</td>
<td>Inflammatory</td>
</tr>
<tr>
<td>Pituitary adenoma</td>
<td>Tumours (55% of all spinal tumours): lymphoma, metastases (lymphoma, lung, breast, prostate), neurofibroma</td>
<td>Tumours</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pus/inflammation</td>
<td>Blood</td>
<td></td>
</tr>
<tr>
<td>Cerebral abscess, extradural abscess, subdural empyema</td>
<td>Extracranial extramedullary</td>
<td></td>
</tr>
<tr>
<td>Encephalitis (see Infectious Diseases, ID18)</td>
<td>Vascular: dural arteriovenous fistula, subdural hematomas (especially if on anticoagulants)</td>
<td></td>
</tr>
<tr>
<td>Tumefactive MS</td>
<td>Tumours (40% of all spinal tumours): meningioma, schwannoma, neurofibroma</td>
<td></td>
</tr>
<tr>
<td>Blood</td>
<td>Extracranial intramedullary</td>
<td></td>
</tr>
<tr>
<td>Extradural (epideral) hematomas</td>
<td>Tumours (5% of all spinal tumours): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids</td>
<td></td>
</tr>
<tr>
<td>Subdural hematomas</td>
<td>Syringomyelia (common causes: trauma, congenital, idiopathic)</td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage: SAH, ICH, IVH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyst</td>
<td>Intradural extramedullary</td>
<td></td>
</tr>
<tr>
<td>Arachnoid cyst</td>
<td>Tumours (5% of all spinal tumours): astrocytomas and ependymomas most common; also hemangioblastomas and dermoids</td>
<td></td>
</tr>
<tr>
<td>Dermoid cyst</td>
<td>Syringomyelia (common causes: trauma, congenital, idiopathic)</td>
<td></td>
</tr>
<tr>
<td>Epidermoid cyst</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colloid cyst (3rd ventricle)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## INTRACRANIAL PATHOLOGY

### Intracranial Pressure Dynamics

Table 1. Approach to Intracranial Pathology

<table>
<thead>
<tr>
<th>Issue</th>
<th>Time Frame</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular</td>
<td>Sudden</td>
<td>No H/A = occlusive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>H/A = hemorrhagic</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Hours to days</td>
<td>Affects entire CNS</td>
</tr>
<tr>
<td>Infectious</td>
<td>Days to weeks</td>
<td>Often a source of infection on history</td>
</tr>
<tr>
<td>Tumor</td>
<td>Months</td>
<td>Increased ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Initially + H/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Constant</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Progressive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Severe</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Worse in morning</td>
</tr>
<tr>
<td></td>
<td></td>
<td>As ICP increases:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Blurry vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Projectile vomiting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Severely raised ICP:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Cushing’s reflex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• HTN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Respiratory changes</td>
</tr>
</tbody>
</table>

Table 2. Consequences of Common Brain Lesions

<table>
<thead>
<tr>
<th>Location of Lesion</th>
<th>Consequence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal lobe</td>
<td>1. Disinhibition</td>
</tr>
<tr>
<td></td>
<td>2. Concentration deficits</td>
</tr>
<tr>
<td></td>
<td>3. Orientation deficits</td>
</tr>
<tr>
<td></td>
<td>4. Judgment defects</td>
</tr>
<tr>
<td></td>
<td>5. ± Primitive reflex re-emergence</td>
</tr>
<tr>
<td></td>
<td>6. ± Contralateral motor deficits if motor cortex involved</td>
</tr>
<tr>
<td>Broca’s area</td>
<td>1. Non-fluent aphasia</td>
</tr>
<tr>
<td>(inferior frontal</td>
<td>2. Repetition impaired</td>
</tr>
<tr>
<td>gyrus of dominant</td>
<td>3. Comprehension relatively spared</td>
</tr>
<tr>
<td>hemisphere)</td>
<td></td>
</tr>
<tr>
<td>Wernicke’s area</td>
<td>1. Fluent aphasia</td>
</tr>
<tr>
<td>(superior temporal</td>
<td>2. Repetition impaired</td>
</tr>
<tr>
<td>gyrus of dominant</td>
<td>3. Comprehension markedly impaired</td>
</tr>
<tr>
<td>hemisphere)</td>
<td></td>
</tr>
<tr>
<td>Occipital lobe</td>
<td>Contralateral visual field deficits</td>
</tr>
<tr>
<td>Right parietal lobe</td>
<td>Hemispatial neglect syndrome</td>
</tr>
<tr>
<td></td>
<td>• Contralateral agnosia</td>
</tr>
<tr>
<td>Basal ganglia</td>
<td>1. Rest tremor</td>
</tr>
<tr>
<td></td>
<td>2. Chorea</td>
</tr>
<tr>
<td></td>
<td>3. Athetosis</td>
</tr>
<tr>
<td>Subthalamic nucleus</td>
<td>Contralateral hemiballismus</td>
</tr>
<tr>
<td>Mammillary bodies</td>
<td>Wernicke-Korsakoff syndrome</td>
</tr>
<tr>
<td>(bilateral)</td>
<td>1. Wernicke</td>
</tr>
<tr>
<td></td>
<td>• Confusion</td>
</tr>
<tr>
<td></td>
<td>• Ophthalmoplegia</td>
</tr>
<tr>
<td></td>
<td>• Ataxia</td>
</tr>
<tr>
<td></td>
<td>2. Korsakoff</td>
</tr>
<tr>
<td></td>
<td>• Anterograde amnesia</td>
</tr>
<tr>
<td></td>
<td>• Confabulation</td>
</tr>
<tr>
<td></td>
<td>• Personality changes</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Anterograde amnesia</td>
</tr>
<tr>
<td>Reticular activating system (midbrain)</td>
<td>Reduced levels of arousal and wakefulness</td>
</tr>
<tr>
<td>Paramedian pontine reticular formation</td>
<td>Gaze deviation away from side of lesion</td>
</tr>
<tr>
<td>Frontal eye fields</td>
<td>Gaze deviation toward side of lesion</td>
</tr>
<tr>
<td>Cerebellar hemisphere</td>
<td>1. Intention tremor</td>
</tr>
<tr>
<td></td>
<td>2. Limb ataxia</td>
</tr>
<tr>
<td></td>
<td>3. Fall towards side of lesion</td>
</tr>
<tr>
<td>Cerebellar vermis</td>
<td>1. Truncal ataxia</td>
</tr>
<tr>
<td></td>
<td>2. Dysarthria</td>
</tr>
</tbody>
</table>
ICP/Volume Relationship

- adult skull is rigid with a constant intracranial volume
- contents (CSF, blood, brain) are incompressible (Monro-Kellie doctrine)
- increase in one constituent/space-occupying lesion = 1) increase in ICP, 2) require redistribution of CSF, blood, or brain
- however, ICP does not rise initially due to compensatory mechanisms
  - immediate: displacement of CSF to lumbar theca, displacement of blood from venous sinuses
  - delayed: displacement of ECF or ICF, displacement of brain tissue into compartments under less pressure (herniation)
- once compensation is exhausted, ICP rises exponentially

Cerebral Blood Flow

- brain receives about 15% of cardiac output (~750 mL/min)
- CBF depends on cerebral perfusion pressure (CPP) and cerebral vascular resistance (CVR)
- normal CPP >50 mmHg in adults
- cerebral autoregulation maintains constant CBF by compensating for changes in CPP, unless:
  - high ICP such that CPP <60 mmHg
  - MAP >150 mmHg or MAP <50 mmHg
  - brain injury: e.g. SAH, severe trauma

ICP Measurement

- normal ICP <15 mmHg (8-18 cmH2O) for adult, 3-7 mmHg (4-9.5 cmH2O) for child; varies with patient position
  - moderate elevation: increase in mean pressure >20 mmHg
  - severe elevation: increase in mean pressure >40 mmHg
- waveform: comprised of respiratory and cardiac pulsations (Traube-Hering waves); the amplitude increases with ICP
  - β-waves: coarse, variably increased amplitude, frequency ½-2/min, often related to respiration
  - plateau waves: elevation of ICP over 50 mmHg lasting 5-20 min, precursor of further deterioration

Acute Monitoring

- lumbar puncture (LP)
- intraventricular catheter/ventriculostomy/external ventricular drain (EVD) ("gold standard", also permits therapeutic drainage of CSF to decrease ICP)

Chronic Monitoring

- fibreoptic monitor (intraventricular, intraparenchymal, subdural), subarachnoid bolt (Richmond screw), and epidural monitor

Elevated ICP

Etiology

- intracranial space-occupying lesion
  - tumour
  - pus
  - blood (trauma → hematoma [most common], subarachnoid hemorrhage)
  - depressed skull fracture
  - foreign body
- increased intracranial blood volume
  - vasodilatation (increased pCO₂/decreased pO₂/decreased extracellular pH, e.g. hypoventilation)
  - venous outflow obstruction (venous sinus thrombosis, superior vena cava syndrome, space-occupying lesion)
  - cranial dependency
- cerebral edema
  - vasogenic (vessel damage, e.g. hypertensive encephalopathy, tumour)
  - cytotoxic (tissue/cell death, e.g. hypoxia, brain injury)
  - osmotic (acute hyponatremia, hepatic encephalopathy)
• hydrocephalus
  ▪ obstructive: acquired aqueductal stenosis
  ▪ non-obstructive: decreased CSF absorption with SAH
• pseudotumour cerebri (idiopathic intracranial HTN)
• impaired autoregulation (hypotension, HTN, brain injury)
• status epilepticus (chronic seizure resulting in brain edema)

Clinical Features
1. Acute Elevated ICP
• H/A: worse in the morning, aggravated by stooping, and bending
• N/V
• decreased LOC if ICP = dBP, or midbrain compressed
• drop in GCS = best index to monitor progress and predict outcome of acute intracranial process (see Neurotrauma, NS29)
• papilledema ± retinal hemorrhages (may take 24-48 h to develop)
• abnormal extra-ocular movements (EOM)
  ▪ CN VI palsy: often falsely localizing (causative mass may be remote from nerve)
  ▪ upward gaze palsy (especially in children with obstructive hydrocephalus)
• herniation syndromes
• focal signs/symptoms due to lesion

2. Chronic Elevated ICP
• H/A postural: worsened by coughing, straining, and bending over
• morning/evening H/A → vasodilatation due to increased CO₂ with recumbency
• visual changes
  ▪ due to papilledema
  ▪ enlarged blind spot, if advanced → episodic constrictions of visual fields (“grey-outs”)
  ▪ optic atrophy/blindness
  ▪ differentiate from papillitis (usually unilateral with decreased visual acuity)
• decreased level of consciousness

Investigations
• patients with suspected elevated ICP require an urgent CT/MRI
• ICP monitoring where appropriate

Table 3. Herniation Syndromes

<table>
<thead>
<tr>
<th>Herniation Syndrome</th>
<th>Definition</th>
<th>Etiology</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Subfalcine</td>
<td>Cingulate gyrus herniates under falx</td>
<td>Lateral supratentorial lesion</td>
<td>Usually asymptomatic</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Warnings of impending transtentorial herniation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Risk of ACA compression</td>
</tr>
<tr>
<td>2. Central Tentorial (Axial)</td>
<td>Displacement of diencephalon through tentorial notch</td>
<td>Supratentorial midline lesion, Diffuse cerebral swelling, Late uncinal herniation</td>
<td>Small pupils, moderately dilated, fixed (rostral to caudal deterioration), sequential failure of diencephalon, medulla</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decreased LOC (midbrain compression), EOM/ upward gaze impairment (“sunset eyes”): compression of pretectum and superior colliculi</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Brainstem herniation (“Duret’s” – secondary to shearing of basilar artery perforating vessels)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Diabetes insipidus (traction on pituitary stalk and hypothalamus), end-stage sign</td>
</tr>
<tr>
<td>3. Lateral Tentorial (Uncal)</td>
<td>Uncus of temporal lobe herniates down through tentorial notch</td>
<td>Lateral supratentorial lesion (often rapidly expanding traumatic hematoma)</td>
<td>Ipsilateral non-reactive dilated pupil (earliest, most reliable sign) + ipsilateral EOM paralysis, ptosis (CN III compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decreased LOC (midbrain compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Contralateral hemiplegia ± extensor (upgoing) plantar response ± ipsilateral hemiplegia (“Kernohan’s notch” – a false localizing sign resulting from pressure from the edge of the tentorium on the contralateral cerebral peduncle)</td>
</tr>
<tr>
<td>4. Upward</td>
<td>Cerebellar vermis herniates through tentorial incisura</td>
<td>Large posterior fossa mass (common after VP shunting)</td>
<td>Cerebellar infarct (superior cerebellar artery (SCA) compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Hydrocephalus (cerebral aqueduct compression)</td>
</tr>
<tr>
<td>5. Tonsillar</td>
<td>Cerebellar tonsils herniate through foramen magnum</td>
<td>Infratentorial lesion, Following central tentorial herniation, Following LP in presence of intracranial mass lesion</td>
<td>Neck stiffness and head tilt (tonsillar impaction)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Decreased LOC (midbrain compression)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Flaccid paralysis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Respiratory irregularities, respiratory arrest (compression of medullary respiratory centres)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Blood pressure instability (compression of medullary cardiovascular centres)</td>
</tr>
</tbody>
</table>

Figure 6. Herniation types

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**Treatment of Elevated ICP**

- CT or MRI to identify etiology, assess for midline shift/herniation
- treat primary cause (i.e. remove mass lesions, ensure adequate ventilation)
- if elevated ICP persists following treatment of primary cause, consider therapy when ICP >20 mmHg
- goals: keep ICP <20 mmHg, CPP >65 mmHg, MAP >90 mmHg

**Conservative Measures**

- elevate head of bed at 30°, maintain neck in neutral position → increases intracranial venous outflow with minimal effect on arterial pressure
- prevent hypotension with fluid and vasopressors, dopamine, norepinephrine prn
- ventilate to normocarbia (pCO₂ 35-40 mmHg) → prevents vasodilatation
- oxygen to maintain pO₂ >60 mmHg → prevents hypoxic brain injury
- osmolar diuresis (mannitol 20% IV solution 1-1.5 g/kg, then 0.25 g/kg q6h to serum osmolarity of 315-320)
  - can give rapidly, acts in 15-30 min, must maintain sBP >90 mmHg
  - corticosteroids → decrease edema over subsequent days around brain tumor, abscess, blood
  - no proven value in head injury or stroke

**Aggressive Measures**

- sedation (“light” e.g. barbiturates/codeine → “heavy” e.g. fentanyl/MgSO₄)
- paralysis with vecuronium → reduces sympathetic tone, reduces HTN induced by muscle contraction
- hyperventilate to pCO₂ 30-35 mmHg
  - use for brief periods only – also results in decreased cerebral blood flow
- drain 3-5 mL CSF via ventricles, assess each situation independently
- insert EVD (if acute) or shunt
- barbiturate-induced coma induced with pentobarbital to reduce cerebral blood flow and metabolism (10 mg/kg over 30 min, then 1 mg/kg q1h continuous infusion)
  - decreases mortality, but no improvement in neurological outcome
- decompressive craniectomy is a last resort
- no role for the use of hypothermia in head injury

**Hydrocephalus**

- hydrocephalus in children, see *Pediatric Neurosurgery*, NS35

**Definition**

- accumulation of excess CSF in the brain
- CSF: produced by choroid plexus lateral ventricles
- total volume ~120 mL, including 30 cc within ventricular system, remainder in SA space
- flow: lateral ventricle → foramina of Luschka (lateral) and Magendie (medial) → subarachnoid space
- re-absorbed by arachnoid villi into dural venous sinuses

**Etiology**

- congenital versus acquired
- obstruction to CSF flow
- decreased CSF absorption
- increased CSF production (rarely) – e.g. choroid plexus papilloma (0.4-1% of intracranial tumours)

**Epidemiology**

- estimated prevalence 1-1.5%; incidence of congenital hydrocephalus ~1-2/1,000 live births
Classification

Table 4. Classification of Hydrocephalus

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Definition</th>
<th>Etiology</th>
<th>Findings on CT/MRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive (Non-Communicating) Hydrocephalus</td>
<td>Circulation blocked within ventricular system proximal to the arachnoid granulations</td>
<td>Acquired</td>
<td>Ventricular enlargement proximal to block</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Aqueductal stenosis (adhesions following infection, hemorrhage)</td>
<td>Periventricular hypodensity (transepidermal migration of CSF forced into extracellular space)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Intraventricular lesions (tumours e.g. 3rd ventricle colloid cyst, hematoma)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mass causing tentorial herniation, aqueduct/4th ventricle compression</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: neurosarcoidosis, abscess/ granulomas, arachnoid cysts</td>
<td></td>
</tr>
<tr>
<td>Congenital</td>
<td></td>
<td>Aqueductal stenosis, Dandy-Walker malformation, Chiari malformation (see Pediatric Neurosurgery, NS34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ventricular enlargement proximal to block</td>
<td></td>
</tr>
<tr>
<td>Non-Obstructive (Communicating) Hydrocephalus</td>
<td>CSF absorption blocked at extraventricular site = arachnoid granulations</td>
<td>Post-infectious (#1 cause) menigitis, cystercerosis</td>
<td>All ventricles dilated</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Post-hemorrhagic (#2 cause) SAH, RH, traumatic</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Choroid plexus papilloma (rare, causes increased CSF production)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Idiopathic → normal pressure hydrocephalus</td>
<td></td>
</tr>
<tr>
<td>Normal Pressure Hydrocephalus (NPH)</td>
<td>Persistent ventricular dilatation in the context of normal CSF pressure</td>
<td>Idiopathic (50%)</td>
<td>Enlarged ventricles without increased prominence of cerebral sulci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Others: subarachnoid hemorrhage, meningitis, trauma, radiation-induced</td>
<td></td>
</tr>
<tr>
<td>Hydrocephalus Ex Vacuo</td>
<td>Ventricular enlargement resulting from atrophy of surrounding brain tissue</td>
<td>Normal aging</td>
<td>Enlarged ventricles and sulci</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Alzheimer's, Creutzfeldt-Jacob Disease</td>
<td>Cerebral atrophy</td>
</tr>
</tbody>
</table>

Clinical Features

- acute hydrocephalus
  - signs and symptoms of acute elevated ICP (see Elevated ICP, NS5)
  - impaired upward gaze ("sunset eyes") and/or CN VI palsy
- chronic/gradual onset hydrocephalus (i.e. NPH)
  - gradual onset of classic triad developing over weeks or months
    - pressure of ventricle on lower extremity motor fibres → gait disturbance (ataxia and apraxia usually initial symptoms)
    - pressure on cortical bowel/bladder centre → urinary incontinence
    - pressure on frontal lobes → dementia
  - CSF pressure can be measured within clinically “normal” range

Investigations

- CT/MRI (periventricular lucency suggests raised CSF pressure)
- ultrasound (through anterior fontanelle in infants)
- ICP monitoring (e.g. LP) may be used to investigate NPH, test response to shunting (lumbar tap test)
- radionuclide cisternography can test CSF flow and absorption rate (unreliable)
- β-2 transferrin assay to test for the presence of CSF leak

Treatment

- ventricular drainage
- surgical removal of obstruction (if possible) or excision of choroid plexus papilloma
- shunts
  - ventriculoperitoneal (VP): most common
  - ventriculopleural
  - ventriculo-atrial (VA): relatively increased risk of infections, shunt emboli
  - lumboperitoneal: for communicating hydrocephalus and pseudotumour cerebri
- third ventriculostomy (for obstructive hydrocephalus) via ventriculoscropy
- LPs for transient hydrocephalus (e.g. SAH), IVH in premature infants, etc.
# Shunt Complications

## Table 5. Shunt Complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Obstruction</strong></td>
<td>• Obstruction by choroid plexus</td>
<td>• Acute hydrocephalus</td>
<td>• “Shunt series” (plain x-rays of entire shunt that only rule-out disconnection, break, tip migration)</td>
</tr>
<tr>
<td></td>
<td>• Buildup of proteinaceous accretions, blood, cells (inflammatory or tumour)</td>
<td>• Increased ICP</td>
<td>• CT</td>
</tr>
<tr>
<td></td>
<td>• Infection</td>
<td></td>
<td>• Radionuclide “shuntogram”</td>
</tr>
<tr>
<td></td>
<td>• Disconnection or damage</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Acute hydrocephalus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Increased ICP</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Shunt nephritis (VA shunt)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td>• S. epidermidis</td>
<td>• Fever, N/V, anorexia, irritability</td>
<td>• CBC</td>
</tr>
<tr>
<td>(3-6%)</td>
<td>• S. aureus</td>
<td>• Meningitis</td>
<td>• Blood culture</td>
</tr>
<tr>
<td></td>
<td>• P. acne</td>
<td>• Peritonitis</td>
<td>• Tap shunt for C&amp;S (LP usually NOT recommended)</td>
</tr>
<tr>
<td></td>
<td>• Gram-negative bacilli</td>
<td>• Signs and symptoms of shunt obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Shunt nephritis (VA shunt)</td>
<td></td>
</tr>
<tr>
<td><strong>Overshunting</strong></td>
<td>• Slit ventricle syndrome, collapse of ventricles leading to occlusion of shunt ports by ependymal lining</td>
<td>• Chronic or recurring headaches often relieved when lying down</td>
<td>• CT/MRI</td>
</tr>
<tr>
<td>(10% over 6-5 yr)</td>
<td>• Subdural hematoma</td>
<td>• Asymptomatic</td>
<td>• Slit-like ventricles on imaging</td>
</tr>
<tr>
<td></td>
<td>• Collapsing brain tears bridging veins (especially common in NPH patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Secondary craniosynostosis (children): apposition and overlapping of the cranial sutures in an infant following decompression of hydrocephalus</td>
<td>• Abnormal head shape</td>
<td>• Clinical</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• CT</td>
</tr>
<tr>
<td><strong>Seizures</strong></td>
<td>• Increased intraperitoneal pressure/fluid results in hernia becoming apparent</td>
<td>• Inguinal swelling, discomfort</td>
<td>• EEG</td>
</tr>
<tr>
<td>(5.5% risk in 1st yr, 1.1% after 3rd yr)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inguinal Hernia</strong></td>
<td>• Increased intraperitoneal pressure/fluid results in hernia becoming apparent</td>
<td></td>
<td>• U/S</td>
</tr>
<tr>
<td>(17% incidence with VP shunt inserted in infancy) ± skin breakdown over hardware</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

## Idiopathic Intracranial Hypertension (Pseudotumour Cerebri)

### Definition
- Raised intracranial pressure and papilledema without evidence of any mass lesion, hydrocephalus, infection, or hypertensive encephalopathy (diagnosis of exclusion)

### Etiology
- Unknown (majority), but associated with
  - Lateral venous sinus thrombosis
  - Habitus/diet: obesity, hyper/hypovitaminosis A
  - Endocrine: reproductive age, menstrual irregularities, Addison’s/Cushing’s disease, thyroid irregularities
  - Hematological: iron deficiency anemia, polycythemia vera
  - Drugs: steroid administration or withdrawal, tetracycline, nalidixic acid, etc.
- Risk factors overlap with those of venous sinus thrombosis; similar to those for gallstones (“fat, female, fertile, forties”)

### Epidemiology
- Incidence ~0.5/100,000 per year
- Usually in 3rd and 4th decade (F>M)

### Clinical Features
- Symptoms and signs of raised ICP (H/A in >90%, pulsatile intracranial noise), but no LOC or diplopia
- Decreased visual acuity, papilledema, visual field defect, optic atrophy (key morbidity)
- Usually self-limited, recurrence is common, chronic in some patients
- Risk of blindness is not reliably correlated to symptoms or clinical course
**Investigations**
- CT: normal
- CSF studies: normal
- MRI: must look for venous sinus thrombosis

**Treatment**
- rule out conditions that cause intracranial HTN (especially sinus thrombosis)
- discontinue offending medications, encourage weight loss, fluid/salt restriction
- pharmacotherapy: acetazolamide (decreases CSF production), thiazide diuretic, or furosemide
- if above fail: serial LPs, shunt
- optic nerve sheath decompression (if progressive impairment of visual acuity)
- 2 yr follow-up with imaging to rule out occult tumour, ophthalmology follow-up

---

### Tumours

#### Classification
- primary vs. metastatic, intra-axial (parenchymal) vs. extra-axial, supratentorial vs. infratentorial, adult vs. pediatric
- benign: non-invasive, but can be devastating due to expansion of mass in fixed volume of skull (mass effect)
- malignant: implies rapid growth, invasiveness, but rarely extracranial metastasis
- types of intracranial tumours (* = most common)
  - neuroepithelial tissue
    - astrocytic tumours: astrocytoma, glioblastoma
  - oligodendroglial tumours
  - oligoastrocytic tumours
  - neuronal and mixed neuronal-glial tumours: ganglion cell tumours, cerebral neurocytomas/neuroblastosomas
  - embryonal tumours: medulloblastoma, neuroectodermal
  - other: pineal, ependymal, and choroid plexus tumours
  - meningeal: meningiomas*, mesenchymal, hemangioblastomas
  - cranial and paraspinous nerves: schwannoma, neurofibroma
  - lymphomas and hematopoietic neoplasms
  - germ cell: germinomas, teratomas
  - pituitary adenomas
  - sellar region: craniopharyngiomas, spindle cell oncocytoma
  - cysts: epidermoid/dermoid cysts, colloid cysts
  - local extension: chordomas, glomus jugulare tumours
  - metastatic tumours

#### Clinical Features
- supratentorial lesions
  - progressive neurological deficit (70%)
  - frontal lobe: hemiparesis, dysphasia, personality changes, cognitive changes
  - temporal lobe: auditory/olfactory hallucinations, memory deficits, contralateral superior quadrantanopsia

---

### DDx for Ring Enhancing Lesion on CT with Contrast

- Lesions (+ edema, necrosis, hemorrhage)
- Midline shifts and herniations
- Effacement of ventricles and sulci (often ipsilateral), basal cisterns
- Single or multiple (multiple implies metastasis)

---

**Primary Sources of Metastatic Brain Tumours**

- Lung: 44%
- Breast: 10%
- Kidney (RCC): 7%
- GI: 6%
- Melanoma: 3%

**Primary CNS lymphoma** reported in 5-20% of HIV infected patients

**Brain Metastasis**

- ~1/3 of all adult brain tumours
- Well circumscribed, often at grey-white matter junction
• symptoms suggestive of TIA (occlusion of vessel by tumour cells or 2nd "steal phenomenon" where blood is shunted from ischemic regions to non-ischemic regions and manifested as neurological changes)
• endocrine disturbances with pituitary tumours (e.g. Cushing’s disease, prolactinoma)
• rarely presents with hemorrhage

**Intracranial lesions**
- most commonly presents with signs of elevated ICP
  - headache
  - nausea and vomiting
  - papilledema
- diplopia (direct compression CN VI versus indirect compression from increased ICP)
- vertigo
- ataxia (due to cerebellar lesions)

**Familial syndromes associated with CNS Tumours**
- von Hippel-Lindau (hemangioblastoma of brain, spinal cord, and eye)
- tuberous sclerosis (giant cell astrocytoma, cortical tubers, and suppengydral nodules)
- neurofibromatosis type 1 and 2 (astrocytoma, bilateral acoustic neuroma respectively)
- Li-Fraumeni (astrocytoma)
- Turcot syndrome (glioblastoma multiforme)
- multiple endocrine neoplasia type 1 (MEN-1) (pituitary adenoma)

**Investigations**
- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic workup

**Treatment**
- conservative: serial Hx, Px, imaging for slow growing/benign lesions
- medical: corticosteroids to reduce cytotoxic cerebral edema, pharmacological (see *Pituitary Adenoma*, NS13)
- surgical: total or partial excision (decompressive, palliative), shunt if hydrocephaus
- radiotherapy: conventional fractionated radiotherapy (XRT), stereotactic radiosurgery (e.g. Gamma Knife®)
- chemotherapy: e.g. alkylating agents (temozolomide)

**Investigations**
- CT, MRI, stereotactic biopsy (tissue diagnosis), metastatic workup

**Class I – Karnofsky performance status (KPS) ≥ 80**

Three prognostic groups based on 1,200 patients:
- Class I – Karnofsky performance status (KPS) > 80 yr with controlled primary (3 mo stability on imaging or newly diagnosed), no extracranial metastases (median survival 7.1 mo).
- Class II – everything else (median survival 4.2 mo).
- Class III – KPS < 70 (median survival 2.3 mo).

**Summary of Evidence for Single and Multiple Brain Metastases**
1) For patients with good performance status (e.g. KPS > 70), limited extracranial disease and resectable metastases, complete resection improves the probability of extended survival. WBRT in addition to resection improves local and overall brain control but does not affect overall survival or duration of functional independence.
2) For patients with a good prognosis (>3 mo expected survival), single brain metastases < 4 cm in size, good performance status, and controlled extracranial disease, the addition of radiosurgery to WBRT improves survival when compared with WBRT alone.
3) In patients with a good prognosis and up to 4 brain metastases < 4 cm in size, radiosurgery added to WBRT improves lesion site and overall brain control compared with WBRT alone, but does not influence survival. Therefore, WBRT alone may be considered in these patients.
4) The use of radiosurgery boost to WBRT may improve KPS and decrease the need for steroids at 6 mo in patients with up to 3 brain metastases.
5) For selected patients with poor life expectancy (< 3 mo), the use of WBRT may or may not significantly improve symptoms from brain metastases. Corticosteroids, or short course (20 Gy in 5 daily fractions) WBRT are reasonable options.
6) There is no evidence of a survival benefit with the combined use of radiosensitizers with WBRT.
7) Although chemotherapy trials have reported improved response rates with combined chemotherapy and WBRT, the addition of chemotherapy leads to increased toxicity and does not improve survival. The routine use of chemotherapy in the management of brain metastases is not generally recommended.

**Metastatic Tumours**
- most common brain tumour seen clinically
- 15-30% of cancer patients present with cerebral metastatic tumours
- most common sources: lungs, breast
- other sources: kidney, thyroid, stomach, prostate, testis, melanoma
- hematogenous spread most common

**Location**
- 80% are hemispheric, often at grey-white matter junction or junction of temporal-parietal-occipital lobes (likely emboli spreading to terminal MCA branches)

**Investigations**
- identify primary tumour
- metastatic workup (CXR, CT chest/abdo, abdominal U/S, bone scan, mammogram)
- CT with contrast → round, well-circumscribed, often ring enhancing, ++ edema, often multiple
- MRI more sensitive, especially for posterior fossa
- consider biopsy in unusual cases, or if no primary identified
Treatment
• medical
  □ phenytoin (or levetiracetam) for seizure prophylaxis if patient presents with seizure
  □ dexamethasone to reduce edema given with ranitidine
  □ chemotherapy (e.g. small cell lung cancer)
• radiation
  □ stereotactic radiosurgery: for discrete, deep-seated/inoperable tumours
  □ multiple lesions: use WBRT; consider stereotactic radiosurgery if <3 lesions
  □ post-operative WBRT is commonly used
• surgical
  □ single/solitary lesions: use surgery and radiation

Prognosis
• median survival without treatment once symptomatic is ~1 mo, with optimal treatment 6-9 mo but varies depending on primary tumour type

Astrocytoma
• most common primary intra-axial brain tumour, common in 4th-6th decades

Table 7. Astrocytoma Grading System

<table>
<thead>
<tr>
<th>World Health Organization (WHO)</th>
<th>Typical CT/MRI Findings</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I – Pilocytic astrocytoma</td>
<td>± mass effect, ± enhancement</td>
<td>&gt;10 yr, cure if gross total resection</td>
</tr>
<tr>
<td>II – Low grade/diffuse</td>
<td>Mass effect, no enhancement</td>
<td>5 yr</td>
</tr>
<tr>
<td>III – Anaplastic</td>
<td>Complex enhancement</td>
<td>1.5-2 yr</td>
</tr>
<tr>
<td>IV – Glioblastoma multiforme (GBM)</td>
<td>Necrosis (ring enhancement)</td>
<td>12 mo, 10% at 2 yr</td>
</tr>
</tbody>
</table>

Clinical Features
• sites: cerebral hemispheres >> cerebellum, brainstem, spinal cord
• symptoms: recent onset of new/worsening H/A, N/V, seizure, ± focal deficits or symptoms of increased ICP

Investigations
• CT/MRI with contrast: variable appearance depending on grade
• hypodense on CT, hypointense on T1 MRI, hyperintense on T2 MRI
• low grade: most do not enhance and have calcification on CT
• high grade: most enhance with CT contrast dye/gadolinium

Treatment
• low grade diffuse astrocytoma
  □ close follow-up; radiation, chemotherapy, and surgery all valid options
  □ surgery: not curative, trend towards better outcomes
  □ radiotherapy alone or post-operative prolongs survival (retrospective evidence)
  □ chemotherapy; usually reserved for tumour progression
• high grade astrocytomas (anaplastic astrocytoma and GBM)
  □ surgery
    □ gross total resection: maximal safe resection + fractionated radiation with 2 cm margin + concomitant and adjuvant temozolomide
    □ except: extensive dominant lobe GBM, significant bilateral involvement, end-of-life near, extensive brainstem involvement
    □ stereotactic biopsy if resection not possible, followed by fractionated radiation with 2 cm margin
  □ expectant (based on functional impairment – Karnofsky score <70; patient’s/family’s wishes)
  □ aim to prolong “quality” survival
  □ chemotherapy: ~20% response rate, temozolomide (agent of choice); better response to temozolomide predicted by MGMT gene hypermethylation
• multiple gliomas: WBRT ± chemotherapy

Meningioma
• most common primary intracranial tumour, arise from arachnoid membrane
• often calcified, cause hyperostosis of adjacent bone
• classically see Psammoma bodies on histology
• common locations: parasagittal convexity or falx (70%), sphenoid wing, tuberculum sellae, foramen magnum, olfactory groove

WHO Classification of Meningioma (by histology)
Grade 1: low risk of recurrence
Grade 2: intermediate risk of recurrence
Grade 3: high risk of recurrence

Figure 10. High grade astrocytoma on CT

Bevacizumab Plus Radiotherapy-Temozolomide for Newly Diagnosed Glioblastoma

Purpose: To evaluate the effect of combined bevacizumab and radiotherapy-temozolomide in the treatment of newly diagnosed glioblastoma.

Study: Patients with supratentorial glioblastoma randomly assigned to receive intravenous bevacizumab or placebo plus radiotherapy and oral temozolomide for 30 wk total n cycles, followed by bevacizumab or placebo monotherapy. Outcomes were progression-free survival and overall survival.

Results: 458 patients in bevacizumab group, 463 patients in placebo. The median progression-free survival was longer in the bevacizumab group although there was a higher frequency of adverse events.

Conclusions: Early surgical resection of low grade gliomas is associated with better overall survival as compared to watchful waiting.
Clinical Features
- middle aged, slight female preponderance (M:F = 2:3), high progesterone receptors (increase in size with pregnancy), symptoms of increased ICP, focal deficits, usually solitary (10% multiple, likely with loss of NF2 gene/22q12 deletion)

Investigations
- CT with contrast: homogeneous, densely enhancing, along dural border ("dural tail"), well circumscribed
- contrast enhanced MRI provides better detail
- angiography
  - most are supplied by external carotid feeders (meningeal vessels)
  - also assesses venous sinus involvement, "tumour blush" commonly seen (prolonged contrast image)
- octreotide scintigraphy: to establish if expression of somatostatin receptor

Treatment
- conservative management for non-progressive, asymptomatic lesions
- surgery is treatment of choice if symptomatic or progression on sequential imaging (curative if complete resection)
- SRS may be an option for lesions <3 cm
- endovascular embolization to facilitate surgery
- SRS or XRT for recurrent atypical/malignant meningiomas

Prognosis
- >90% 5-yr survival, recurrence rate variable (often ~10-20%)
- depends on extent of resection (Simpson's classification)

Vestibular Schwannoma (Acoustic Neuroma)
- slow-growing (average of 1-10 mm/yr), benign posterior fossa tumour
- arises from vestibular component of CN VIII in internal auditory canal, expanding into bony canal and cerebello-pontine angle (CPA)
- if bilateral, diagnostic of neurofibromatosis type II
- epidemiology: all age groups affected, peaks at 4th-6th decades

Clinical Features
- compression of structures in CPA, often CN VIII (unilateral hearing loss 98%, tinnitus, disequilibrium), followed by CN V and VII
- ataxia and raised ICP are late features

Investigations
- MRI with gadolinium or T2 FIESTA sequence (>98% sensitive/specific), CT with contrast 2nd choice
- audiogram, brainstem auditory evoked potentials, caloric tests

Treatment
- conservative: serial imaging (CT/MRI q6mo) and audiometry
- radiation: stereotactic radiosurgery or fractionated radiotherapy
- surgery if: lesion >3 cm, brainstem compression, edema, hydrocephalus
  - curable if complete resection (almost always possible)
  - operative complications: CN VII, VIII dysfunction (only significant disability if bilateral), CSF leak

Pituitary Adenoma
- primarily from anterior pituitary, 3rd-4th decades, M=F
- incidence in autopsy studies approximately 20%
- classification
  - microadenoma <1 cm; macroadenoma ≥1 cm
  - endocrine active (functional/secretory) vs. inactive (non-functional)
    - most common functional: prolactinomas, adrenocorticotropic, growth-hormone producing
  - differential: parasellar tumours (e.g. craniopharyngioma, tuberculum sellae meningioma), carotid aneurysm
Clinical Features
- mass effects
  - H/A
  - bitemporal hemianopsia (compression of optic chiasm)
  - CN III, IV, V1, V2, VI palsy (compression of cavernous sinus)
- endocrine effects
  - hyperprolactinemia (prolactinoma): infertility, amenorrhea, galactorrhea, decreased libido
  - ACTH production: Cushing’s disease, hyperpigmentation
  - GH production: acromegaly/gigantism
  - panhypopituitarism (hypothyroidism, hypoadrenalism, hypogonadism)
  - associated MEN-1 syndrome
  - diabetes insipidus
- pituitary apoplexy (sudden expansion of mass due to hemorrhage or necrosis)
  - abrupt onset H/A, visual disturbances, ophthalmoplegia, reduced mental status, and panhypopituitarism
- CSF rhinorrhea and seizures (rare)
- signs and symptoms of subarachnoid hemorrhage (rare)

Investigations
- formal visual fields, CN testing
- endocrine tests (prolactin level, TSH, 8 AM cortisol, fasting glucose, FSH/LH, IGF-1), electrolytes, urine electrolytes, and osmolarity
- imaging (MRI with and without contrast)

Treatment
- medical
  - for apoplexy: rapid corticosteroid administration ± surgical decompression
  - for prolactinoma: dopamine agonists (e.g. bromocriptine)
  - for Cushing’s: serotonin antagonist (cyproheptadine), inhibition of cortisol production (ketoconazole)
  - for acromegaly: somatostatin analogue (octreotide) ± bromocriptine
  - endocrine replacement therapy
- surgical
  - trans-sphenoidal, trans-ethmoidal, trans-cranial approaches for non-secreting adenomas causing mass effect and Cushing/acromegaly (50% cure rate)

Pus

Sources of Pus/Infection
- four routes of microbial access to CNS
  1. hematogenous spread (most common): arterial and retrograde venous
    - adults: chest is #1 source (lung abscess, bronchiectasis, empyema)
    - children: congenital cyanotic heart disease with R to L shunt
    - immunosuppression (AIDS – toxoplasmosis)
  2. direct implantation (dural disruption)
    - trauma
    - iatrogenic (e.g. following LP, post-operative)
    - congenital defect (e.g. dermal sinus)
  3. contiguous spread (adjacent infection): from air sinus, naso/oropharynx, surgical site
    - (e.g. otitis media, mastoiditis, sinusitis, osteomyelitis, dental abscess)
  4. spread from PNS (e.g. viruses: rabies, herpes zoster)
- common examples
  - epidural abscess: in cranial and spinal epidural space, associated with osteomyelitis
  - treatment: immediate drainage and antibiotics, surgical emergency if cord compression
  - subdural empyema: bacterial/fungal infection, due to contiguous spread from bone or air sinus, progresses rapidly
  - treatment: surgical drainage and antibiotics, 20% mortality
- meningitis, encephalitis (see Infectious Diseases, ID18)
- cerebral abscess

Cerebral Abscess

Definition
- pus in brain substance, surrounded by tissue reaction (capsule formation)

Etiology
- modes of spread: 10-60% of patients have no cause identified
- pathogens
  - *Streptococcus* (most common), often anaerobic or microaerophilic
  - *Staphylococcus* (penetrating injury)
  - Gram-negatives, anaerobes (*Bacteroides, Fusobacterium*)
  - in neonates: *Proteus* and *Citrobacter* (exclusively)
- immunocompromised: fungi and protozoa (Toxoplasma, Nocardia, Candida albicans, Listeria monocytogenes, Mycobacterium, and Aspergillus)

Risk Factors
- lung abnormalities (infection, AV fistulas; especially Osler-Weber-Rendu syndrome [i.e. hereditary hemorrhagic telangiectasia])
- congenital coronary heart disease: R-to-L shunt bypasses pulmonary filtration of micro-organisms
- bacterial endocarditis
- penetrating head trauma
- immunosuppression (e.g. AIDS)
- dental abscess

Clinical Features
- focal neurological signs and symptoms
  - H/A, decreased LOC; hemiparesis and seizures in 50%
  - mass effect, increased ICP and sequelae (cranial enlargement in children)
  - hemiparesis and seizures in 50%
  - ± signs and symptoms of systemic infection (low-grade fever, leukocytosis)

Complications
- with abscess rupture: ventriculitis, meningitis, venous sinus thrombosis
- CSF obstruction
- transtentorial herniation

Investigations
- CT scan often first test in emergency department
- MRI
  - imaging of choice
  - apparent diffusion coefficient (ADC) used to differentiate abscess (black) from tumour (white)
- WBC/ESR may be normal, blood cultures rarely helpful and LP contraindicated if large mass
- CSF: non-specific (high ICP, high WBC, high protein, normal carbohydrate), rarely helpful, usually negative culture

Treatment
- aspiration ± excision and send for Gram stain, acid fast bacillus (AFB), C&S, fungal culture
- excision preferable if location suitable
- antibiotics
  - empirically: vancomycin + ceftriaxone + metronidazole or chloramphenicol or rifampin (6-8 wk therapy)
  - revise antibiotics when C&S known
- anti-convulsants (1-2 yr)
- follow-up CT is critical (do weekly initially, more frequent if condition deteriorates)

Prognosis
- mortality with appropriate therapy ~10%, permanent deficits in ~50%

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### Blood

Table 8. Comparison of Epidemiology and Etiology of Intracranial Bleeds

<table>
<thead>
<tr>
<th>Types of Hematoma/ Hemorrhage</th>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>CT Features</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidural Hematoma</td>
<td>Skull fracture causing middle meningeal bleed</td>
<td>M&gt;F (4:1), associated with trauma</td>
<td>Lucid interval before LOC</td>
<td>Hyperdense lenticular mass with sharp margins, usually limited by suture lines</td>
<td>Craniotomy</td>
<td>Good with prompt management (Note: respiratory arrest can occur from uncal herniation)</td>
</tr>
<tr>
<td>Acute SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, associated with trauma</td>
<td>No lucid interval, hemiparesis, pupillary changes</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Craniotomy if bleed &gt; 1 cm thick</td>
<td>Poor</td>
</tr>
<tr>
<td>Chronic SDH</td>
<td>Ruptured subarachnoid bridging vessels</td>
<td>Age &gt;50, EtOH abusers, anti-coagulated</td>
<td>Often asymptomatic, minor H/A, confusion, signs of increased ICP</td>
<td>Hyperdense crescentic mass, crossing suture lines</td>
<td>Burr hole to drain; craniotomy if recurs</td>
<td>Good</td>
</tr>
<tr>
<td>SAH</td>
<td>Trauma, spontaneous (aneurysms, idiopathic, AVM)</td>
<td>Age 55-60; 20% cases under age 45</td>
<td>Sudden onset thunderclap H/A, signs of increased ICP</td>
<td>Hyperdense blood in cisterns/fissures (sensitivity decreases over time)</td>
<td>Conservative: NPO, IV NS, ECG, Foley, BP 120-150, vasospasm prophylaxis (nimodipine); open vs. endovascular surgery to repair if rebleed</td>
<td>Poor: 50% mortality; 30% of survivors have moderate to severe disability</td>
</tr>
<tr>
<td>ICH</td>
<td>HTN, vascular abnormality, tumours, infections, coagulopathy</td>
<td>Age &gt;55, male, drug use (cocaine, EtOH, amphetamine)</td>
<td>TIA-like symptoms, signs of increased ICP</td>
<td>Hyperdense intraparenchymal collection</td>
<td>Medical: decrease BP, control ICP Surgical: craniotomy</td>
<td>Poor: 44% mortality due to cerebral herniation</td>
</tr>
</tbody>
</table>
Extradural ("Epidural") Hematoma

Etiology
- temporal-parietal skull fracture: 85% are due to ruptured middle meningeal artery; remainder of cases are due to bleeding from middle meningeal vein, dural sinus, or bone/diploic veins

Epidemiology
- young adult, M>F = 4:1; rare before age 2 or after age 60
- 1-4% of traumatic head injuries

Clinical Features
- classic sequence (seen in <30%): post-traumatic reduced LOC, a lucid interval of several hours, then obtundation, hemiparesis, ipsilateral pupillary dilatation, and coma
- signs and symptoms depend on severity but can include H/A, N/V, amnesia, altered LOC, aphasia, seizures, HTN, and respiratory distress
- deterioration can take hours to days

Investigations
- CT without contrast: "lenticular-shaped" usually limited by suture lines but not limited by dural attachments

Treatment
- admission, close neurological observation with serial CT indicated if all of the following are present
  - small volume clot, minimal midline shift (MLS <5 mm), GCS >8, no focal deficit
  - otherwise, craniotomy to evacuate clot, follow up CT
  - mannitol pre-operative if elevated ICP or signs of brain herniation

Prognosis
- good with prompt management, as the brain is often not damaged
- worse prognosis if bilateral Babinski or decerebration pre-operative
- death is usually due to respiratory arrest from uncal herniation (injury to the midbrain)

Subdural Hematoma

ACUTE SUBDURAL HEMATOMA
- 1-2 d after bleeding onset

Etiology
- rupture of vessels that bridge the subarachnoid space (e.g. cortical artery, large vein, venous sinus) or cerebral laceration

Risk Factors
- trauma, acceleration-deceleration injury, anticoagulants, alcohol, cerebral atrophy, infant head trauma

Clinical Features
- no lucid period, signs and symptoms can include altered LOC, pupillary irregularity, hemiparesis

Investigations
- CT: hyperdense concave "crescentic" mass, crossing suture lines

Treatment
- craniotomy if clinically symptomatic, if hematoma >1 cm thick, or if MLS >5 mm (optimal if surgery <4 h from onset); otherwise observe with serial imaging

Prognosis
- poor overall since the brain parenchyma is often injured (mortality range is 50-90%, due largely to underlying brain injury)
- prognostic factors: initial GCS and neurologic status, post-operative ICP

Use of Drains vs. No Drains After Burr-Hole Evacuation of Chronic Subdural Hematoma: A Randomized Control Trial

Purpose: To examine the effect of drains on recurrence rates of chronic subdural hematoma (SDH) and clinical outcomes.

Study: RCT with 269 patients ≥18 yr of age with chronic SDH. Half of the patients were randomly assigned to receive a subdural drain and the other half no drain after evacuation.

Results: Recurrence occurred in 9.3% of people with a drain and 24% without (p=0.003; 95% CI 0.14-0.70). Although rates of complications were the same between the study groups, mortality at 6 mo was 8.6% in the group receiving a drain and 18.1% in the group not receiving a drain (p=0.042; 95% CI 0.1-0.99).

Conclusions: Use of drains after burr-hole drainage of chronic SDH is safe and associated with a reduced recurrence and mortality at 6 mo.
CHRONIC SUBDURAL HEMATOMA
• ≥15 d after bleeding onset

Etiology
• many start out as acute SDH
• blood within the subdural space evokes an inflammatory response:
  ▪ fibroblast invasion of clot and formation of neomembranes within days → growth of neocapillaries → fibrinolysis and liquefaction of blood clot (forming a hygroma)
• course is determined by the balance of rebleeding from neomembranes and resorption of fluid

Risk Factors
• older, alcoholics, patients with CSF shunts, anticoagulants, coagulopathies

Clinical Features
• often due to minor injuries or no history of injury
• may present with minor H/A, confusion, language difficulties, TIA-like symptoms, symptoms of raised ICP ± seizures, progressive dementia, gait problem
• obtundation disproportionate to focal deficit; “the great imitator” of dementia, tumours

Investigations
• CT: hypodense (liquefied clot), crescentic mass

Treatment
• seizure prophylaxis only if post-traumatic seizure
• reverse coagulopathies
• burr hole drainage of liquefied clot indicated if symptomatic or thickness >1 cm; craniotomy if recurs more than twice

Prognosis
• good overall as brain usually undamaged, but may require repeat drainage

Cerebrovascular Disease

Ischemic Cerebral Infarction (80%)
• embolic, thrombosis of intracerebral arteries, vasculitis, hypercoagulability, etc. (see Neurology, N50)

Intracranial Hemorrhage (20%)
• SAH, spontaneous ICH, IVH

Figure 15. Subdural hematoma on CT

Figure 16. Aneurysms of the Circle of Willis

Types of Aneurysms
Saccular  Fusiform  Dissecting

1. Anterior communicating artery, 30%
2. Middle cerebral artery, 20%
3. Internal carotid/posterior communicating artery, 30%
4. Basilar tip, 7%
5. Superior cerebellar artery, 3%
6. Vertebobasilar junction, 2%
7. Posterior inferior cerebellar artery, 3%

Hemicraniectomy in Older Patients with Extensive Middle-Cerebral-Artery Stroke
NEJM 2014;370:1091-1100

Purpose: To determine if early decompressive hemicraniectomy reduces mortality among patients >60 yr.

Study: 112 patients >60 yr (median age 70 yr) with malignant MCA infarction randomly assigned to conservative ICU treatment versus hemicraniectomy. Endpoint was survival without severe disability (modified Rankin scale score 0-4).

Results: The proportion of patients who survived without severe disability was 38% in the hemicraniectomy group and 18% in the control group (OR 2.91, 95% CI 1.06-7.49). Modified Rankin scale scores in hemicraniectomy versus control group in terms of percentages of patients:
  - 0-2 (0%, 0%), 3 or moderate disability (7%, 3%), 4 or moderate severe disability (32%, 19%), 5 or severe disability (23%, 13%) and 6 or death (33%, 70%). Infections were more frequent in the hemicraniectomy group and herniation more frequent in the control group.

Conclusions: Hemicraniectomy increased survival without severe disability among patients >60 yr with a malignant MCA infarction.
Subarachnoid Hemorrhage

Definition
- bleeding into subarachnoid space (intracranial vessel between arachnoid and pia)

Etiology
- trauma (most common)
- spontaneous
  - ruptured aneurysms (75-80%)
  - idiopathic (14-22%)
  - AVMs (4-5%)
- coagulopathies (iatrogenic or primary), vasculitides, tumours, cerebral artery dissections (<5%)

Epidemiology
- ~10-28/100,000 population/yr
- peak age 55-60, 20% of cases occur under age 45

Risk Factors
- HTN
- pregnancy/parturition in patients with pre-existing AVMs, eclampsia
- oral contraceptive pill
- substance abuse (cigarette smoking, cocaine, alcohol)
- conditions associated with high incidence of aneurysms (see Intracranial Aneurysms, NS21)

Clinical Features of Spontaneous SAH
- sudden onset (seconds) of severe "thunderclap" H/A usually following exertion and described as the "worst headache of my life" (up to 97% sensitive, 12-25% specific)
- N/V, photophobia
- meningismus (neck pain/stiffness, positive Kernig's and Brudzinski's sign)
- decreased LOC (due to either raised ICP, ischemia, seizure)
- focal deficits: cranial nerve palsies (CN III, IV), hemiparesis
- ocular hemorrhage in 20-40% (due to sudden raised ICP compressing central retinal vein)
- reactive HTN
- sentinel bleeds
  - represents undiagnosed SAH
  - SAH-like symptoms lasting <1 d ("thunderclap H/A")
  - may have blood on CT or LP
  - ~30-60% of patients with full blown SAH give history suggestive of sentinel bleed within past 3 wk
- differential diagnosis: sentinel bleed, dissection/thrombosis of aneurysm, venous sinus thrombosis, benign cerebral vasculitis, benign exertional H/A

Investigations
- non-contrast CT - for diagnosis of SAH
  - 98% sensitive within 12 h, 93% within 24 h; 100% specificity
  - may be negative if small bleed or presentation delayed several days
  - acute hydrocephalus, IVH, ICH, infarct or large aneurysm may be visible
- lumbar puncture (highly sensitive) - for diagnosis of SAH if CT negative but high suspicion:
  - elevated opening pressure (>18 cmH2O)
  - bloody initially, xanthochromic supernatant with centrifugation ("yellow") by ~12 h, lasts 2 wk
  - RBC count usually >100,000/mm³ without significant drop from first to last tube (in contrast to traumatic tap)
  - elevated protein due to blood breakdown products
- four vessel cerebral angiography ("gold standard" for aneurysms)
  - demonstrates source of SAH in 80-85% of cases
  - angiogram negative SAH: repeat angiogram in 7-14 d, if negative \( \Rightarrow \) "perimesencephalic SAH"
- MRA and CTA: sensitivity up to 95% for aneurysms, CTA>MRA for smaller aneurysms and delineating adjacent bony anatomy

Hunt and Hess Grade
(clinical grading scale for SAH)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Sx or mild H/A and/or mild meningismus</td>
</tr>
<tr>
<td>2</td>
<td>Grade 1 + CN palsy</td>
</tr>
<tr>
<td>3</td>
<td>Confusion/lethargy, mild hemiparesis, or aphasia</td>
</tr>
<tr>
<td>4</td>
<td>GCS &lt; 15 but &gt; 8, moderate-severe hemiparesis, mild rigidity</td>
</tr>
<tr>
<td>5</td>
<td>Coma (GCS &lt; 9), decerebrate, moribund appearance</td>
</tr>
</tbody>
</table>

Mortality of Grade 1-2 20%, increased with grade

World Federation of Neurological Surgeons Grading of SAH

<table>
<thead>
<tr>
<th>WFNS Grade</th>
<th>GCS Score</th>
<th>Aphasia, Hemiparesis, or Hemiplegia</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 *</td>
<td>15</td>
<td>-</td>
</tr>
<tr>
<td>1</td>
<td>13-14</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>13-14</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>7-12</td>
<td>+ or -</td>
</tr>
<tr>
<td>4</td>
<td>3-6</td>
<td>+ or -</td>
</tr>
</tbody>
</table>

*Intact aneurysm
Figure 17. Diagnosis of SAH

<table>
<thead>
<tr>
<th>Fisher Grade (SAH on CT scan)</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal scan</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1 mm thick blood</td>
</tr>
<tr>
<td>3</td>
<td>&gt;1 mm thick blood</td>
</tr>
<tr>
<td>4</td>
<td>SAH + ICH or IVH</td>
</tr>
</tbody>
</table>

"Triple H" Therapy for Vasospasm

HTN
Hypervolemia
Hemodilution

Calcium Antagonists for Aneurysmal Subarachnoid Hemorrhage

Introduction: This study looked to review the evidence in regards to whether calcium antagonists improve the outcome in patients with aneurysmal subarachnoid hemorrhage.

Methods/Population: The review included 3,361 patients presenting with aneurysmal subarachnoid hemorrhage from 16 RCTs comparing treatment with calcium antagonists vs. control from 1980 to March 2006.

Results: The results were based mainly on one large trial of oral nimodipine, which showed a RR of 0.67 (95% CI 0.55-0.81) and the evidence for other calcium agents was not statistically significant.

Conclusion: The authors endorse the use of oral nimodipine in patients with aneurysmal subarachnoid hemorrhage.

Complications

- vasospasm: vasoconstriction and permanent pathological vascular changes in response to vessel irritation by blood – can lead to delayed cerebral ischemia and death
  - onset: 4-14 d post-SAH, peak at 6-8 d; most commonly due to SAH, rarely due to ICH/IVH
  - clinical features (new onset ischemic deficit): confusion, decreased LOC, focal deficit (speech or motor e.g. pronator drift)
  - risk factors: large amount of blood on CT (high Fisher grade), smoking, increased age, HTN
  - "symptomatic" vasospasm in 20-30% of SAH patients
  - "radiographic" vasospasm in 30-70% of arteriograms performed 7 d following SAH
  - diagnosed clinically, and/or with transcranial Doppler (increased velocity of blood flow)
  - risk of cerebral infarct and death
  - treatment
    - hyperdynamic ("triple H") therapy using fluids and pressors, usually after ruptured aneurysm has been clipped/coiled
    - direct vasodilation via angioplasty or intra-arterial verapamil for refractory cases
    - hydrocephalus (15-20%): due to blood obstructing arachnoid granules
    - can be acute or chronic, requires extraventricular drain (EVD) or shunt, respectively
    - neurogenic pulmonary edema

Treatment

- admit to ICU or NICU
  - oxygen/ventilation prn
  - NPO, bed rest, elevate head of bed 30°, minimal external stimulation, neurological vitals q1h
  - aim to maintain sBP = 120-150 (balance of vasospasm prophylaxis, risk of re-bleed, risk of hypotension since CBF autoregulation impaired by SAH)
  - cardiac rhythm monitor, Foley prn, strict monitoring of ins and outs
- medications
  - IV NS with 20 mmol KCl/L at 125-150 cc/h
  - nimodipine 60 mg PO/NG q4h x 21 d for delayed cerebral ischemia neuroprotection; may discontinue earlier if patient is clinically well
  - seizure prophylaxis: levetiracetam (Keppra®) 500 mg PO/IV q12h x 1 wk
  - mild sedation prn

Background: Two rules for SAH diagnosis exist. A clinical prediction rule states that patients with acute severe H/A but without the clinical variables age ≥40 yr, neck pain, loss of consciousness, or onset of H/A with exertion are at low risk for SAH. An imaging prediction rule bases diagnosis on non-contrast cranial CT for patients within 6 h of H/A onset.

Methods: Matched case-control study of 55 patients at 21 emergency departments between 2000 and 2011, and diagnoses were verified by lumbar puncture.

Results: The clinical prediction rule for diagnosis of SAH was 97.1% sensitive, 22.7% specific, and had a negative likelihood ratio of 0.13. Using the imaging prediction rule resulted in a false negative rate of 20%.

Conclusions: Performing the clinical and imaging rules together has the potential for maximizing sensitivity of prediction and reducing rates of lumbar puncture, but using imaging alone can result in missed cases.
hyponatremia: due to cerebral salt wasting (increased renal sodium loss and ECFV loss), not SIADH
• diabetes insipidus
• cardiac: arrhythmia (>50% have ECG changes), MI, CHF

Prognosis
• 10-15% mortality before reaching hospital, overall 50% mortality (majority within first 2-3 wk)
• 30% of survivors have moderate to severe disability
• a major cause of mortality is rebleeding, for untreated aneurysms:
  ▪ risk of rebleed: 4% on first day, 15-20% within 2 wk, 50% by 6 mo
  ▪ if no rebleed by 6 mo, risk decreases to same incidence as unruptured aneurysm (2%)
  ▪ only prevention is early clipping or coiling of “cold” aneurysm
  ▪ rebleed risk for “perimesencephalic SAH” is approximately same as for general population

Intracerebral Hemorrhage

Definition
• hemorrhage within brain parenchyma, accounts for ~10% of strokes
• can dissect into ventricular system (IVH) or through cortical surface (SAH)

Etiology
• HTN (usually causes bleeds at putamen, thalamus, pons, and cerebellum)
• hemorrhagic transformation (reperfusion post stroke, surgery, strenuous exercise, etc.)
• vascular anomalies
  ▪ aneurysm, AVMs, and other vascular malformations (see Vascular Malformations, NS22)
  ▪ venous sinus thrombosis
  ▪ arteriopties (cerebral amyloid angiopathy, lipohyalinosis, vasculitis)
• tumours (1%): often malignant (e.g. GBM, lymphoma, metastases)
• drugs (amphetamine, cocaine, alcohol, anticoagulants, etc.)
• coagulopathy (iatrogenic, leukemia, TTP, aplastic anemia)
• CNS infections (fungal, granulomas, herpes simplex encephalitis)
• post trauma (immediate or delayed, frontal and temporal lobes most commonly injured via coup-contrecoup mechanism)
• eclampsia
• post-operative (post-carotid endarterectomy cerebral reperfusion, craniotomy)
• idiopathic

Epidemiology
• 12-15 cases/100,000 population/yr

Risk Factors
• increasing age (mainly >55 yr)
• male gender
• HTN
• Black/Asian > Caucasian
• previous CVA of any type (23x risk)
• both acute and chronic heavy alcohol use; cocaine, amphetamines
• liver disease
• anticoagulants

Clinical Features
• TIA-like symptoms often precede ICH, can localize to site of impending hemorrhage
• gradual onset of symptoms over minutes-hours, usually during activity
• H/A, N/V, and decreased LOC are common
• specific symptoms/deficits depend on location of ICH

Investigations
• hyperdense blood on non-contrast CT
• CTA routine, if spot sign demonstrated there is high likelihood of clot growth

Treatment
• medical
  ▪ decrease MAP to pre-morbid level or by ~20% (target BP 140/90)
  ▪ check PTT/INR, and correct coagulopathy
  ▪ control raised ICP (see Intracranial Pressure Dynamics, NS4)
  ▪ levetiracetam/phenytoin for seizure prophylaxis
  ▪ follow electrolytes (SIADH common)
  ▪ angiogram to rule out vascular lesion unless >45 yr, known HTN, and putamen/thalamic/ posterior fossa ICH (yield ~0%)
surgical
- craniotomy with evacuation of clot, treatment of source of ICH (i.e. AVM, tumour, cavernoma), ventriculostomy to treat hydrocephalus
- indications
  - symptoms of raised ICP or mass effect
  - rapid deterioration (especially if signs of brainstem compression)
  - favourable location (e.g. cerebellar, non-dominant hemisphere)
  - young patient (<50 yr)
  - if tumour, AVM, aneurysm, or cavernoma suspected (resection or clip to decrease risk of rebleed)
- contraindications
  - small bleed: minimal symptoms, GCS >10
  - poor prognosis: massive hemorrhage (especially dominant lobe), low GCS/coma, lost brainstem function
  - medical reasons (e.g. very elderly, severe coagulopathy, difficult location [e.g. basal ganglia, thalamus])

Prognosis
- 30-d mortality rate 44%, mostly due to cerebral herniation
- rebleed rate 2-6%, higher if HTN poorly controlled

### Intracranial Aneurysms

#### Epidemiology
- prevalence 1-4% (20% have multiple)
- F>M; age 35-65 yr

#### Risk Factors
- autosomal dominant polycystic kidney disease (15%)
- fibromuscular dysplasia (7-21%)
- AVMs
- connective tissue diseases (Ehlers-Danlos, Marfan)
- family history
- bacterial endocarditis
- Osler-Weber-Rendu syndrome (hereditary hemorrhagic telangiectasia)
- atherosclerosis and HTN
- trauma

#### Types
- saccular (berry)
  - most common type
  - located at branch points of major cerebral arteries (Circle of Willis)
- 85-95% in carotid (anterior) system, 5-15% in vertebrobasilar (posterior) circulation
- fusiform
  - atherosclerotic
  - more common in vertebrobasilar system, rarely rupture
- infectious
  - secondary to any infection of vessel wall, 20% multiple
- 60% Streptococcus and Staphylococcus
- 3-15% of patients with bacterial endocarditis

### Table 9. Five Year Cumulative Rupture Risk in Unruptured Aneurysms Based on Size and Location

<table>
<thead>
<tr>
<th>Size</th>
<th>Cavernous Carotid</th>
<th>AC/MC/IC</th>
<th>Vertebrobasilar/PC/PComm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7 mm</td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td>7-12 mm</td>
<td>0%</td>
<td>2.6%</td>
<td>14.5%</td>
</tr>
<tr>
<td>13-24 mm</td>
<td>3%</td>
<td>14.5%</td>
<td>18.4%</td>
</tr>
<tr>
<td>≥24 mm</td>
<td>6.4%</td>
<td>40%</td>
<td>50%</td>
</tr>
</tbody>
</table>

**AC** = anterior cerebral/anterior communicating artery; **IC** = internal carotid artery; **MC** = middle cerebral artery; **PC** = posterior cerebral artery; **PCComm** = posterior communicating artery

**Clinical Presentation**
- rupture (90%), most often SAH, 20% ICH, 3% subdural bleed
- sentinel hemorrhage (‘thunderclap H/A’) → requires urgent clipping/coiling to prevent catastrophic bleed
- mass effect (giant aneurysms)
  - internal carotid or anterior communicating aneurysm may compress:
    - the pituitary stalk or hypothalamus causing hypopituitarism
    - the optic nerve or chiasm producing a visual field defect
  - basilary artery aneurysm may compress midbrain, pons (limb weakness), or CN III
  - posterior communicating artery aneurysm may produce CN III palsy
  - intracavernous aneurysms (CN III, IV, V1, V2, VI)

---

**Risk of Recurrent Subarachnoid Hemorrhage, Death, or Dependence and Standardized Mortality Ratios after Clipping or Coiling of an Intracranial Aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): Long-Term Follow-Up**

**Objective:** To assess the long-term risk of death, disability, and rebleeding in patients randomly assigned to clipping or endovascular coiling after rupture of an intracranial aneurysm in the follow-up of the ISAT trial.

**Methods:** Randomized controlled trial comparing endovascular coiling treatment with craniotomy and clipping for ruptured intracranial aneurysms in 2,143 patients who were considered eligible for either modality of therapy. Annual follow-up was done for a mean length of 9 yr to assess long-term survival and dependency.

**Results:** 10 patients in the coiled group and 3 patients in the clipped group had rebleed from the original aneurysm. In patients with ruptured intracranial aneurysm, survival the survival rate at 5 yr after endovascular coiling was higher at 89% vs. 85% for neurosurgical clipping (relative risk 0.77, p=0.03). The likelihood of independence at 5 yr following treatment is the same for both groups (83% for clipping vs. 82% for clipping).

**Conclusion:** The risk of death at 5 yr was significantly lower in the clipped group than it was in the coiled group. There was a small increased risk of recurrent bleeding from a coiled aneurysm compared with a clipped aneurysm.

---

**Long-Term, Serial Screening for Intracranial Aneurysms in Individuals with a Family History of Aneurysmal Subarachnoid Hemorrhage: A Cohort Study**

**Purpose:** To examine the yield of long-term serial screening for intracranial aneurysms for individuals with a positive family history of aneurysmal subarachnoid hemorrhage (aSAH) (two or more first-degree relatives who have had aSAH or unruptured intracranial aneurysms).

**Study:** Screening results from April 1 1993 to April 1 2013 were reviewed in a cohort study. MRA or CTA was done from age 16-18 to 65-70 yr. After a negative screen, individuals were advised to contact the clinic in 5 yr for follow up.

**Results:** Aneurysms were identified in 11% of individuals at first screening (n=450), 8% at second screening (n=281), 5% at third screening (n=128), and 5% at fourth screening (n=63). Smoking (OR 2.7, 95% CI 1.2-5.9), history of previous aneurysms (3.8, 95% CI 1.2-12.3), and familial history of aneurysms (3.5, 1.8-6.1) were significant risk factors for aneurysms at first screening. History of previous aneurysms was the only significant risk factor for aneurysms at follow-up screening (HR 4.5, 95% CI 1.1-18.7).

**Conclusion:** The benefit of long-term screening in individuals with a family history of aSAH is substantial up to and after 10 yr of follow-up and two initial negative screens.
- distal embolization (e.g. amaurosis fugax)
- seizures
- I/H/A (without hemorrhage)
- incidental CT or angiography finding (asymptomatic)

Investigations
- CT angiogram (CTA), magnetic resonance angiography (MRA), cerebral angiogram

Treatment
- ruptured aneurysms
  - overall trend towards better outcome with early surgery or coiling (48-96 h after SAH)
  - treatment options: surgical placement of clip across aneurysm neck, trapping (clipping of proximal and distal vessels), thrombosing using Guglielmi detachable coils (coiling) or flow diversion stents, wrapping (last resort)
  - choice of surgery vs. coiling not yet well defined, consider location, size, shape, and tortuosity of the aneurysm, patient comorbidities, age, and neurological condition. In general:
    - coiling: posterior > anterior circulation, deep/eloquent location, basilar artery bifurcation/apex, older age, presence of comorbidities, presence of vasospasm
    - clipping: superficial > deep, broad aneurysmal base, branching arteries at the aneurysm base, tortuosity/atherosclerosis of afferent vessels, dissection, hematoma, acute brainstem compression
- unruptured aneurysms
  - average 1% annual risk of rupture: risk dependent on size and location of aneurysm
  - no clear evidence on when to operate: need to weigh life expectancy
  - risk of morbidity/mortality of SAH (20%-50%) vs. surgical risk (2%-5%)
  - generally treat unruptured aneurysms >10 mm
  - consider treating when aneurysm 7-9 mm in middle-aged, younger patients or patients with a family history of aneurysms
  - follow smaller aneurysms with serial angiography

Vascular Malformations

Types
- arteriovenous malformations (AVMs)
- cavernous malformations (cavernomas, cavernous hemangiomas/angiomas)
- venous angio\textit{m}a
- capillary telangiectasias
- arteriovenous fistula (AVF) (carotid-cavernous fistula, dural AVF, vein of Galen aneurysm)
- "angiographically occult vascular malformations" (any type, 10% of malformations)

Arteriovenous Malformations

Definition
- tangle of abnormal vessels/arteriovenous shunts, with no intervening capillary beds or brain parenchyma; usually congenital

Epidemiology
- prevalence ~0.14%, M:F = 2:1, average age at diagnosis = 33 yr
- 15-20% of patients with hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome) will have cerebral AVMs

Clinical Features
- hemorrhage (40-60%): small AVMs are more likely to bleed due to direct high pressure AV connections
- seizures (50%): more common with larger AVMs
- mass effect
- focal neurological signs secondary to ischemia (high flow → "steal phenomena")
- localized headache, increased ICP
- bruit (especially with dural AVMs)
- may be asymptomatic ("silent")

Investigations
- MRI (flow void), MRA
- angiography (7%) will have one or more associated aneurysms

Treatment
- decreases risk of future hemorrhage and seizure
  - surgical excision is treatment of choice
  - SRS (stereotactic radiosurgery) is preferred for small (<3 cm) or very deep lesions
  - endovascular embolization (glue, balloon) can be curative (5%) or used as adjuvant to surgery or SRS in larger lesions
  - conservative (e.g. palliative embolization, seizure control if necessary)

Spetzler-Martin AVM Grading Scale

<table>
<thead>
<tr>
<th>Item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td>0-3 cm</td>
<td>1</td>
</tr>
<tr>
<td>3.1-6.0 cm</td>
<td>2</td>
</tr>
<tr>
<td>&gt;6 cm</td>
<td>3</td>
</tr>
<tr>
<td>Location</td>
<td></td>
</tr>
<tr>
<td>Noneloquent</td>
<td>0</td>
</tr>
<tr>
<td>Eloquent</td>
<td>1</td>
</tr>
<tr>
<td>Deep Venous Drainage</td>
<td></td>
</tr>
<tr>
<td>Not present</td>
<td>0</td>
</tr>
<tr>
<td>Present</td>
<td>1</td>
</tr>
</tbody>
</table>

AVM grades calculated by adding the 3 individual Spetzler-Martin Scale scores from the above table. e.g. a 2 cm tumour in noneloquent location without deep venous drainage = Grade I

References
- "Arteriovenous Malformations: A Prospective, Population-Based Cohort Study" by [1]
- "Development of the PHASES Score for Prediction of Risk of Rupture of Intracranial Aneurysms: A Pooled Analysis of Six Prospective Cohort Studies" by [2]
- "Untreated Clinical Course of Cerebral Cavernous Malformations: A Prospective, Population-Based Cohort Study" by [3]

[1]: Lancet Neurol 2012;11:217-224
Prognosis
• 10% mortality, 30-50% morbidity (serious neurological deficit) per bleed
• risk of major bleed in untreated AVMs: 2-4% per year

Cavernous Malformations
• benign vascular hamartoma consisting of irregular sinusoidal vascular channels located within the brain without intervening neural tissue or associated large arteries/veins
• several genes now described: CCM1, CCM2, CCM3
• prevalence of 0.1-0.2%, both sporadic and hereditary forms described

Clinical Features
• seizures (60%), progressive neurological deficit (50%), hemorrhage (20%), H/A
• often an incidental finding
• hemorrhage risk less than AVM, usually minor bleeds

Investigations
• T2WI MRI (non-enhancing) gradient echo sequencing (best for diagnosis)

Treatment
• surgical excision
  • only appropriate for symptomatic lesions that are surgically accessible (supratentorial lesions are less likely to bleed than infratentorial lesions)

EXTRACRANIAL PATHOLOGY

Approach to Limb/Back Pain
• see Orthopedics, OR4

Extradural Lesions

Figure 19. MRI of cavernous malformation
A. T2 weighted imaging MRI
B. Gradient echo sequencing MRI

Figure 20. Vascular supply of spinal cord

Stereotactic Radiosurgery for Cavernous Malformations
J Neurosurg 2000;93:987-989

Introduction: The use of radiosurgery for treatment of cerebral cavernous malformations (CM) is controversial. The safety and efficacy of CM radiosurgery is described.

Methods: Retrospective review of 17 patients with CM who underwent radiosurgery over a 10 yr period. All patients had at least 2 documented hemorrhages prior to therapy.

Results: Annual hemorrhage rate 51 mo preceding surgery was 40.1% compared to 8.8% in first 2 yr after radiosurgery and 2.9% thereafter. However, 41% of patients developed a permanent radiation-related morbidity.

Conclusions: Improbable to conclude that radiosurgery protects patients with CMs against future hemorrhage.
Root Compression

Differential Diagnosis
- herniated disc
- neoplasm (neurofibroma, schwannoma)
- synovial cyst, abscess
- hypertrophic bone/spur

Cervical Disc Syndrome

Etiology
- nucleus pulposus herniates through annulus fibrosus and impinges upon nerve root, most commonly at C6-C7 (C7 root)

Clinical Features
- pain in arm follows nerve root distribution, worse with neck extension, ipsilateral rotation, and lateral flexion (all compress the ipsilateral neural foramen)
- LMN signs and symptoms
- central cervical disc protrusion causes myelopathy as well as nerve root deficits

Investigations
- if red flags: C-spine x-ray, CT, MRI (imaging of choice)
- only consider EMG, nerve conduction studies if diagnosis uncertain and presenting more as peripheral nerve issue

Treatment
- conservative
  - no bedrest unless severe radicular symptoms
  - activity modification, patient education (reduce sitting, lifting)
  - physiotherapy, exercise programs focus on strengthening core muscles
  - analgesics, NSAIDs are more efficacious
  - avoid cervical manipulation, like traction
- surgical indications
  - anterior cervical disectomy is usual approach
  - intractable pain despite adequate conservative treatment for >3 mo
  - progressive neurological deficit

Prognosis
- 95% improve spontaneously in 4-8 wk

<table>
<thead>
<tr>
<th>Table 10. Lateral Cervical Disc Syndromes</th>
</tr>
</thead>
<tbody>
<tr>
<td>C4-5</td>
</tr>
<tr>
<td>Root Involved</td>
</tr>
<tr>
<td>Incidence</td>
</tr>
<tr>
<td>Sensory</td>
</tr>
<tr>
<td>Motor</td>
</tr>
<tr>
<td>Reflex</td>
</tr>
</tbody>
</table>

Cervical Spondylosis

Definition
- progressive degenerative process of cervical spine leading to canal stenosis – congenital spinal stenosis, degeneration of intervertebral discs, hypertrophy of lamina, dura, or ligaments, subluxation, altered mobility, telescoping of the spine due to loss of height of vertebral bodies, alteration of normal lordotic curvature
- resultant syndromes include mechanical neck pain, radiculopathy (root compression), myelopathy (spinal cord compression) and combinations

Epidemiology
- typically begins at age 40-50, M>F, most commonly at the C5-C6 > C6-C7 levels

Pathogenesis
- any of: disc degeneration/herniation, osteophyte formation, ossification, and hypertrophy of ligaments
- pathophysiology includes static compression, dynamic compression, and vascular compromise
Clinical Features
- insidious onset of mechanical neck pain exacerbated by excess vertebral motion (particularly rotation and lateral bending with a vertical compressive force – Spurling’s test)
- the earliest symptoms are gait disturbance and lower extremity weakness or stiffness
- occipital H/A is common
- radiculopathy may involve 1 or more roots, and symptoms include neck, shoulder and arm pain, paresthesias and numbness
- cervical myelopathy may be characterized by weakness (upper > lower extremity), decreased dexterity, and sensory changes
- UMN findings such as hyperreflexia, clonus, and Babinski reflex may be present
- most worrisome complaint is lower extremity weakness (corticospinal tracts)
- myelopathy may be associated with funicular pain, characterized by burning and stinging ± Lhermitte’s sign (lightning-like sensation down the back with neck flexion)

Investigations
- x-ray of cervical spine ± flexion/extension (alignment, fractures)
- MRI most useful for determination of compression of the neural element
- CT is only used for better determination of bony anatomy (i.e. OPLL)
- EMG/nerve conduction studies reserved for peripheral nerve investigation

Treatment
- nonsurgical: prolonged immobilization with cervical bracing (limit movement to minimize cumulative trauma to spinal cord), bed rest, anti-inflammatory medications
- surgical: anterior approach (anterior cervical disectomy or corpectomy), posterior approach (decompressive cervical laminectomy)
- surgical indications: myelopathy with motor impairment, progressive neurologic impairment, intractable pain
- complete remission almost never occurs. Surgical decompression may stop progression of disease

Etiology
- postilaterally herniated disc compressed nerve root exiting BELOW the level of the disc or the traversing nerve root
- far lateral disc herniation compressed nerve root AT the level of the disc or the exiting nerve root
- central herniation causes cauda equina or lumbar stenosis (neurogenic claudication)

Clinical Features
- initially back pain, then leg pain > back pain
- limited back movement (especially forward flexion) due to pain
- motor weakness, dermatomal sensory changes, decreased reflexes
- exacerbation with valsalva; relief with flexing the knee or thigh
- nerve root tension signs
  - straight leg raise (SLR, Lasegue’s test) or crossed SLR (pain should occur at less than 60º) suggests L5, S1 root involvement
  - femoral stretch test suggests L2, L3, or L4 root involvement

Investigations
- MRI is modality of choice
- x-ray spine (only to rule out other lesions), CT (bony anatomy)
- myelogram and post-myelogram CT (only if MRI is contraindicated)

Treatment
- conservative (same as cervical disc disease)
- surgical indications
  - same as cervical disc + cauda equina syndrome

Prognosis
- 95% improve spontaneously within 4-8 wk
- do not follow patients with serial MRIs; clinical status is more important at guiding management

Table 11. Lateral Lumbar Disc Syndromes

<table>
<thead>
<tr>
<th></th>
<th>L3-4</th>
<th>L4-5</th>
<th>L5-S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Root Involved</td>
<td>L4</td>
<td>L5</td>
<td>S1</td>
</tr>
<tr>
<td>Incidence</td>
<td>&lt;10%</td>
<td>45%</td>
<td>45%</td>
</tr>
<tr>
<td>Pain</td>
<td>Femoral pattern</td>
<td>Sciatic pattern</td>
<td>Sciatic pattern</td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial leg</td>
<td>Dorsal foot to hallux</td>
<td>Lateral foot</td>
</tr>
<tr>
<td>Motor</td>
<td>Tibialis anterior (dorsiflexion)</td>
<td>Extensor hallucis longus (hallux extension)</td>
<td>Gastrocnemius, soleus (plantar flexion)</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee jerk</td>
<td>Medial hamstrings</td>
<td>Ankle jerk</td>
</tr>
</tbody>
</table>

Conclusions: Anatomical abnormalities visible on repeated MRI 1 yr after treatment for sciatica due to lumbar-disc herniation could not distinguish patients with resolution of their symptoms from patients still experiencing symptoms.
Table 12. Differentiating Conus Medullaris Syndrome from Cauda Equina Syndrome

<table>
<thead>
<tr>
<th></th>
<th>Conus Medullaris Syndrome</th>
<th>Cauda Equina Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Sudden, bilateral</td>
<td>Gradual, unilateral</td>
</tr>
<tr>
<td><strong>Spontaneous Pain</strong></td>
<td>Rare, if present usually bilateral, symmetric in perineum or thighs</td>
<td>Severe, radicular type: in perineum, thighs, legs, back, or bladder</td>
</tr>
<tr>
<td><strong>Sensory Deficit</strong></td>
<td>Saddle; bilateral and symmetric; sensory dissociation</td>
<td>Saddle; no sensory dissociation; may be unilateral and asymmetric</td>
</tr>
<tr>
<td><strong>Motor Deficit</strong></td>
<td>Symmetric; paraplegia less marked; fasciculations may be present</td>
<td>Asymmetric; paraplegia more marked; atrophy may be present; fasciculations rare</td>
</tr>
<tr>
<td><strong>Reflexes</strong></td>
<td>Only ankle jerk absent (preserved knee jerk)</td>
<td>Knee and ankle jerk may be absent</td>
</tr>
<tr>
<td><strong>Autonomic Symptoms (bladder dysfunction, impotence, etc.)</strong></td>
<td>Urinary retention and atonic anal sphincter prominent early; impotence frequent</td>
<td>Sphincter dysfunction presents late; impotence less frequent</td>
</tr>
</tbody>
</table>

Cauda Equina Syndrome

**Etiology**
- compression or irritation of lumbosacral nerve roots below conus medullaris (below L2 level)
- decreased space in the vertebral canal below L2
- common causes: herniated disc ± spinal stenosis, vertebral fracture, and tumour

**Clinical Features**
- usually acute (develops in less than 24 h); rarely subacute or chronic
- motor (LMN signs)
  - weakness/paraparesis in multiple root distribution
  - reduced deep tendon reflexes (knee or ankle)
- autonomic
  - urinary retention (or overflow incontinence) and/or fecal incontinence due to loss of anal sphincter tone
- sensory
  - low back pain radiating to legs (sciatica) aggravated by Valsalva maneuver and by sitting; relieved by lying down
  - bilateral sensory loss or pain: depends on the level affected
  - saddle area (S2-S5) anesthesia
  - sexual dysfunction (late finding)

**Investigations**
- urgent MRI to confirm compression of S2-S3-S4 nerve root by a large disc herniation
- post-void residual very helpful to determine if true retention is present; volumes controversial but anything over 250 cc in a healthy individual is cause for concerns

**Treatment**
- surgical decompression (<48 h) to preserve bowel, bladder, and sexual function, and/or to prevent progression to paraplegia

**Prognosis**
- markedly improves with surgical decompression
- recovery correlates with function at initial presentation: if patient is ambulatory, likely to continue to be ambulatory; if unable to walk, unlikely to walk after surgery

Lumbar Spinal Stenosis

**Etiology**
- congenital narrowing of spinal canal combined with degenerative changes (herniated disc, hypertrophied facet joints, and ligamentum flavum)

**Clinical Features**
- gradually progressive back and leg pain with standing and walking that is relieved by sitting or lying down (neurogenic claudication – 60% sensitive)
- neurologic exam may be normal, including straight leg raise test

**Investigations**
- MRI is the optimal investigation to confirm and localize the level of stenosis (unlike nerve root compression which can be localized with clinical exam)

**Treatment**
- conservative: NSAIDs, analgesia
- surgical: laminectomy with root decompression (the role of fusion may need to be considered if the amount of bone removed with the laminectomy results in de-stabilization)
Neurogenic Claudication

Etiology
- ischemia of lumbosacral nerve roots secondary to vascular compromise and increased demand from exertion, often associated with lumbar stenosis

Clinical Features
- dermatomal pain/paresthesia/weakness of buttock, hip, thigh, or leg initiated by standing or walking
- slow relief with postural changes (sitting >30 min), NOT simply exertion cessation
- induced by variable degrees of exercise or standing
- may be elicited with lumbar extension, but may not have any other neurological findings, no signs of vascular compromise (e.g. ulcers, poor capillary refill, etc.)

Investigations
- bicycle test may help distinguish neurogenic claudication (NC) from vascular claudication (the waist-flexed individuals on the bicycle with NC can last longer)

Treatment
- same as for lumbar spinal stenosis

Intradural Intramedullary Lesions

Syringomyelia (Syrinx)

Definition
- cystic cavitation of the spinal cord
- presentation is highly variable, usually progresses over months to years
- initially pain, weakness; later atrophy and loss of pain and temperature sensation

Etiology
- 70% are associated with Chiari I malformation, 10% with basilar invagination
- post-traumatic
- tumour
- tethered cord

Clinical Features
- nonspecific features for any intramedullary spinal cord pathology:
  - initially pain, weakness, atrophy, loss of pain and temperature in upper extremities (central syrinx) with progressive myelopathy over years
  - sensory loss with preserved touch and proprioception in a band-like distribution at the level of cervical syrinx
  - sensory loss with preserved touch and proprioception in a band-like distribution at the level of cervical syrinx
  - dysesthetic pain often occurs in the distribution of the sensory loss
  - LMN arm/hand weakness or wasting
  - painless neuropathic arthropathies (Charcot's joints), especially in the shoulder and neck due to loss of pain and temperature sensation

Investigations
- MRI is best method, myelogram with delayed CT

Treatment
- treat underlying cause (e.g. posterior fossa decompression for Chiari I, surgical removal of tumour if causing a syrinx)
- rarely does the syrinx need to be shunted, only when progressive and size allows for insertion of tube

Spinal Cord Syndromes

- spinal cord injury impairment classified according to ASIA score
- ASIA A: complete, no motor/sensory below neurological level including S4/5
- ASIA B: incomplete, sensory but not motor function preserved below neurological level including S4/5
• ASIA C: incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade <3
• ASIA D: incomplete, motor function preserved below neurological level, and more than half of the key muscles below neurological level have a muscle grade 3 or more
• ASIA E: normal motor and sensory function

Complete Spinal Cord Lesion
• bilateral loss of motor/sensory and autonomic function at ≥4 segments below lesion/injury, with UMN signs
• about 3% of patients with complete injuries will develop some recovery within 24 h, beyond 24 h, no distal function will recover

Incomplete Spinal Cord Lesion
• any residual function at ≥4 segments below lesion
• signs include sensory/motor function in lower limbs and “sacral sparing” (perianal sensation, voluntary rectal sphincter contration)

Table 13. Comparison Between Incomplete Spinal Cord Lesion Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Etiology</th>
<th>Motor</th>
<th>Sensory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brown-Séquard</td>
<td>Hemisection of cord</td>
<td>Ipsilateral LMN weakness at the lesion</td>
<td>Ipsilateral loss of vibration and proprioception</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ipsilateral UMN weakness below the lesion</td>
<td>Contralateral loss of pain and temperature</td>
</tr>
<tr>
<td>Anterior Cord</td>
<td>Anterior spinal artery compression or occlusion</td>
<td>Bilateral LMN weakness at the lesion</td>
<td>Preserved light touch</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bilateral UMN weakness below the lesion</td>
<td></td>
</tr>
<tr>
<td>Central Cord (most common)</td>
<td>Syringomyelia, tumours, spinal hyperextention injury</td>
<td>Bilateral motor weakness: Upper limb weakness (LMN lesion) &gt; Lower limb weakness (UMN lesion)</td>
<td>Variable bilateral suspended sensory loss Loss of pain and temperature &gt; loss of vibration and proprioception</td>
</tr>
<tr>
<td>Posterior Cord</td>
<td>Posterior spinal artery infarction, trauma</td>
<td>Preserved</td>
<td>Bilateral loss of vibration, proprioception light touch at and below the lesion Preserved pain and temperature</td>
</tr>
</tbody>
</table>

Peripheral Nerves

• see Neurology, N34

Seddon’s Classification of Peripheral Nerve Injury
• class I: neurapraxia – axon structurally intact but fails to function; recovery within hours to months (average 6-8 wk)
• class II: axonotmesis – axon and myelin sheath disrupted but endoneurium and supporting structures intact → Wallerian degeneration of axon segment distal to injury → spontaneous axonal recovery at 1 mm/d, max at 1-2 yr
• class III: neurotmesis – nerve completely transected, need surgical repair for possibility of recovery
• etiologies: ischemia, nerve entrapment – nerve compressed by nearby anatomic structures, often secondary to localized, repetitive mechanical trauma with additional vascular injury to nerve

Investigations
• neurological exam (power, sensation, reflexes), localization via Tinel’s sign (paresthesias elicited by tapping along the course of a nerve)
• electrophysiological studies (EMG, nerve conduction study) may be helpful in assessing nerve integrity and monitoring recovery, not helpful until 2-3 wk post-injury
• labs: blood work, CSF
• imaging: C-spine, chest/bone x-rays, myelogram, CT, magnetic resonance neurography
• angiogram if vascular damage is suspected

Treatment
• early neurosurgical consultation if injury is suspected
• entrapment
  † conservative: prevent repeated stress/injury, physiotherapy, NSAIDs, local anesthesia/steroid injection
  † surgical: nerve decompression ± transposition for progressive deficits, muscle weakness/atrophy, failure of medical management
• stretch/contusion
  † follow-up clinically for recovery; exploration if no recovery in 3 mo
• axonotmesis
  † if no evidence of recovery, resect damaged segment
  † prompt physical therapy and rehabilitation to increase muscle function, maintain joint range
  of motion, and maximize return of useful function
  † recovery usually incomplete
• neurotmesis
  † surgical repair of nerve sheath unless known to be intact (suture nerve sheaths directly if
  ends approximate or nerve graft [usually sural nerve])
  † clean laceration: early exploration and repair
  † contamination or associated injuries: tag initially with nonabsorbable suture, reapproach
  within 10 d

Complications
• neuropathic pain: with neuroma formation
• complex regional pain syndrome: with sympathetic nervous system involvement

SPECIALTY TOPICS

Neurotrauma

Trauma Management (see Emergency Medicine, ER7)

Indications for Intubation in Trauma
1. depressed LOC (patient cannot protect airway): usually GCS ≤ 8
2. need for hyperventilation
3. severe maxillofacial trauma: patency of airway is doubtful
4. need for pharmacologic paralysis for evaluation or management
   † if basal skull fracture suspected, avoid nasotracheal intubation as may inadvertently enter
   brain
   † note: intubation prevents patient's ability to verbalize for determining GCS

Trauma Assessment

INITIAL MANAGEMENT

ABCs of Trauma Management
• see Emergency Medicine, ER7

NEUROLOGICAL ASSESSMENT

Mini-History
• period of LOC, post-traumatic amnesia, loss of sensation/function, type of injury/accident

Neurological Exam
• GCS
• head and neck (lacerations, bruises, basal skull fracture signs, facial fractures, foreign bodies)
• spine (palpable deformity, midline pain/tenderness)
• eyes (pupillary size and reactivity)
• brainstem (breathing pattern, CN palsies)
• cranial nerve exam
• motor exam, sensory exam (only if GCS is 15), reflexes
• sphincter tone
• record and repeat neurological exam at regular intervals

Investigations
• spinal injury precautions (cervical collar) are continued until C-spine is cleared
• CT/L-spine x-rays
  † AP, lateral, odontoid views for C-spine (must see from C1 to T1; swimmer's view if necessary) or CT
  † rarely done: oblique views looking for pars interarticularis fracture ("Scottie dog" sign)
• CT head and upper C-spine (whole C-spine if patient unconscious) look for fractures, loss
  of mastoid or sinus air spaces, blood in cisterns, pneumocephalus
• cross and type, ABG, CBC, drug screen (especially alcohol)
• chest and pelvic x-ray as indicated

TREATMENT

Treatment for Minor Head Injury
• observation over 24-48 h
• wake every hour
• judicious use of sedatives or pain killers during monitoring period

Glasgow Coma Scale

<table>
<thead>
<tr>
<th>Eye Response</th>
<th>Verbal Response</th>
<th>Motor Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 spontaneous</td>
<td>5 oriented</td>
<td>6 obey commands</td>
</tr>
<tr>
<td>3 opens eyes to voice</td>
<td>4 confused</td>
<td>5 locates to pain</td>
</tr>
<tr>
<td>2 opens eyes to pain</td>
<td>3 inappropriate words</td>
<td>4 withdraws from pain (decrease posturing)</td>
</tr>
<tr>
<td>1 no eye opening</td>
<td>2 incoherent sounds</td>
<td>3 flexes to pain (decrease posturing)</td>
</tr>
<tr>
<td>T intubated</td>
<td>1 no response</td>
<td>1 no response</td>
</tr>
</tbody>
</table>

Best response for each component recorded individually (e.g. E3V3M5)

≥ 13 is mild injury; 9-12 is moderate injury; ≤ 8 is severe injury

Assessment of Spine CT/X-Ray (Parasagittal View)

ABCDs
Alignment (columns: anterior vertebral line, posterior vertebral line, spinolaminar line, posterior spinous line)
Bone (vertebral bodies, facets, spinous processes)
Cartilage
Disc (disc space and interspinous space)
Soft tissues

• Never do lumbar puncture in head injury unless increased ICP has been ruled out
• All patients with head injury have C-spine injury until proven otherwise
• Suspect hematoma in alcoholic-related injuries
• Low BP after head injury means injury elsewhere
• Must clear spine both radiologically AND clinically
Treatment for Severe Head Injury (GCS ≤8)
- clear airway and ensure breathing (if GCS ≤8, intubate)
- secure C-spine
- maintain adequate BP
- monitor for clinical deterioration
- monitor and manage increased ICP if present (see Herniation Syndromes, NS6)

Admission required if:
- skull fracture (indirect signs of basal skull fracture, see Head Injury)
- confusion, impaired consciousness, concussion with >5 min amnesia
- focal neurological signs, extreme H/A, vomiting, seizures
- unstable spine
- use of alcohol
- poor social support

Head Injury

Epidemiology
- M:F = 2-3:1

Pathogenesis
- acceleration/deceleration: contusions, subdural hematoma, axon and vessel shearing/ mesencephalic hemotympanum
- impact: skull fracture, concussion, epidural hematoma
- penetrating: worse with high velocity and/or high missile mass
  - low velocity: highest damage to structures on entry/exit path
  - high velocity: highest damage away from missile tract

Skull Fractures
- depressed fractures: double density on skull x-ray (outer table of depressed segment below inner table of skull), CT with bone window is gold standard
- simple fractures (closed injury): no need for antibiotics, no surgery
- compound fractures (open injury): increased risk of infection, surgical debridement within 24 h is necessary
  - internal fractures into sinus may lead to meningitis, pneumocephalus
  - risk of operative bleed may limit treatment to antibiotics
- basal skull fractures: not readily seen on x-ray; rely on clinical signs
  - retroauricular ecchymoses (Battle’s sign)
  - peri-orbital ecchymoses (raccoon eyes)
  - hemotympanum
- CSF rhinorrhea, otorrhea (suspect CSF if halo or target sign present); suspect with Lefort II/III midface fracture

Cranial Nerve Injury
- most traumatic causes of cranial nerve injury do not warrant surgical intervention
- surgical intervention
  - CN II: local eye/orbit injury
  - CN III, IV, VI: if herniation secondary to mass
  - CN VIII: repair of ossicles
- CN injuries that improve
  - CN I: recovery may occur in a few months; most do not improve
  - CN III, IV, VI: majority recover
  - CN VII: recovery with delayed lesions
  - CN VIII: vestibular symptoms improve over weeks, deafness usually permanent (except when resulting from hemotympanum)

Arterial Injury
- e.g. carotid-cavernous (C-C) fistula, carotid/vertebral artery dissection

Intracranial Bleeding
- see Blood, NS15 and Cerebrovascular Disease, NS17
Brain Injury

Primary Impact Injury
- mechanism of injury determines pathology: penetrating injuries, direct impact
  - low velocity: local damage
  - high velocity: distant damage possible (due to wave of compression), concussion
- concussion: a trauma-induced alteration in mental status
  - American Academy of Neurology (AAN) Classification
  - no parenchymal abnormalities on CT
- coup (damage at site of blow) and contrecoup (damage at opposite site of blow)
  - acute decompression causes cavitation followed by a wave of acute compression
- contusion (hemorrhagic)
  - high density areas on CT ± mass effect
  - commonly occurs with brain impact on bony prominences (inferior frontal lobe, pole of temporal lobe)
- diffuse axonal injury/shearing
  - wide variety of damage results
  - may tear blood vessels (hemorrhagic foci)
  - often the cause of decreased LOC if no space-occupying lesion on CT

Secondary Pathologic Processes
- same subsequent biochemical pathways for each traumatic etiology
- delayed and progressive injury to the brain due to
  - high glutamate release → NMDA receptor activation → cytotoxic cascade
  - cerebral edema
  - intracranial hemorrhages
  - ischemia/infarction
  - raised ICP, intracranial HTN
  - hydrocephalus

Extracranial Conditions
- hypoxemia
  - due to trauma to the chest, upper airway, brainstem
  - extremely damaging to vulnerable brain cells
  - leads to ischemia, raised ICP
- hypercarbia
  - leads to raised ICP (secondary to vasodilation)
- systemic hypotension
  - caused by blood loss (e.g. ruptured spleen)
  - loss of cerebral autoregulation leads to decreased CPP, ischemia
- hyperpyrexia
  - leads to increased brain metabolic demands → ischemia
- fluid and electrolyte imbalance
  - iatrogenic (most common)
  - SIADH caused by head injury
  - diabetes insipidus (DI)
  - may lead to cerebral edema and raised ICP
  - coagulopathy

Intracranial Conditions
- raised ICP due to traumatic cerebral edema OR traumatic intracranial hemorrhage

Brain Injury Outcomes
  - nausea, blurred vision, diplopia, memory impairment, tinnitus, irritability, low concentration; 50% at 6 wk, 14% at 1 yr
- moderately traumatic (GCS 9–12): proportional to age (>40) and CT findings; 60% good recovery, 26% moderately disabled, 7% severely disabled, 7% vegetative/dead
- severe (GCS ≤8): difficult to predict, correlates with post-resuscitation GCS (especially motor) and age

Late Complications of Head/Brain Injury
- seizures: 5% of head injury patients develop seizures
  - incidence related to severity and location of injury (increased with local brain damage or intracranial hemorrhage)
- post-traumatic seizure may be immediate, early, or late
- presence of early (within first wk) post-traumatic seizure raises incidence of late seizures
- meningitis: associated with CSF leak from nose or ear
- hydrocephalus: acute hydrocephalus or delayed normal pressure hydrocephalus (NPH)
Spinal Cord Injury

• see Orthopedics, OR23 and Emergency Medicine, ER9

Neurogenic and Spinal Shock
1. neurogenic shock: hypotension that follows SCI (sBP usually ≤80 mmHg) caused by:
   • interruption of sympathetics (unopposed parasympathetics) below the level of injury
   • loss of muscle tone due to skeletal muscle paralysis below level of injury → venous pooling
   • blood loss from associated wounds (true hypovolemia)
2. spinal shock: transient loss of all neurologic function below the level of the spinal cord injury, causing flaccid paralysis and areflexia for variable periods

Whiplash-Associated Disorders
• definition: traumatic injury to the soft tissue structures in the region of the cervical spine due to hyperflexion, hyperextension, or rotational injury to the neck

Initial Management of SCI
• major causes of death in SCI are aspiration and shock
• the following patients should be treated as having a SCI until proven otherwise:
  • all victims of significant trauma
  • minor trauma patients with decreased LOC or complaints of neck or back pain, weakness, abdominal breathing, numbness/tingling, or priapism

Stabilization and Initial Evaluation in the Hospital
1. ABCs, immobilization (backboard/head strap), oxygenation, Foley catheter to urometer, temperature regulation
2. hypotension: maintain sBP >90 mmHg with pressors (dopamine), hydration, and atropine
   • DVT prophylaxis
3. monitor CBC/electrolytes
4. focused history (see Trauma Assessment, NS29)
5. spine palpation: point tenderness or deformity
6. motor level assessment (including rectal exam for voluntary anal sphincter contraction)
7. sensory level assessment: pinprick, light touch, and proprioception
8. evaluation of reflexes
9. signs of autonomic dysfunction: altered level of perspiration, bowel or bladder incontinence, priapism
10. radiographic evaluation
   • 3 views C-spine x-rays (AP, lateral, and odontoid) to adequately visualize C1 to C7-T1 junction
   • flexion-extension views to disclose occult instability
   • CT scan (bony injuries) typically most trauma centers use CT as the modality of choice for looking at fractures, very sensitive with the high resolution scanners
   • MRI mandatory if neurologic deficits (soft tissue injuries)

Medical Management Specific to SCI
• option: methylprednisolone (given within 8 h of injury) this is controversial and you need to confer with Neurosurgery service
• ± decompression in acute, non-penetrating SCI

Fractures of the Spine

FRACTURES AND FRACTURE-DISLOCATIONS OF THE THORACIC AND LUMBAR SPINE
• assess ligamentous instability using flexion/extension x-ray views of C-spine ± MRI
• thoracolumbar spine unstable if 4/6 segments disrupted (3 columns divided into left and right)
  • anterior column: anterior half of vertebral body, disc, and anterior longitudinal ligament
  • middle column: posterior half of vertebral body, disc, and posterior longitudinal ligament
  • posterior column: posterior arch, facet joints, pedicle, lamina and supraspinous, interspinous, and ligamentum ligaments

Types of Injury (Denis Classification)
• compression fracture (58%)
  • produced by flexion
  • posterior ligament complex (supraspinous and interspinous ligaments, ligamentum flavum, and intervertebral joint capsules) remain intact
  • fractures are stable but lead to kyphotic deformity

Pharmacological Therapy for Acute Spinal Cord Injury: Congress of Neurological Surgeons (CNS) and American Association of Neurological Surgeons (AANS) Guidelines

Introduction: This study sought to determine the relative effectiveness of early (<24 h after injury) versus late (≥24 h after injury) decompressive surgery following a traumatic cervical spinal cord injury (SCI).

Methods/Population: A prospective cohort study completed in 2002-2009 involving 6 North American institutions. Participants were 16-80 yr with a cervical SCI. Outcomes evaluated were changes in American Spinal Injury Association Impairment Scale (ASIS) grade at 6 mo follow-up, complications, and mortality.

Results: Of 313 participants enrolled, 182 underwent early surgery and 131 underwent late surgery. 222 participants were available for follow-up at 6 mo. The odds of at least 2 grade AIS improvement were greater for those who had early surgery compared to those with late surgery (OR = 2.83, 95% CI 1.10, 7.28). Mortality was observed for each group during the first 30 d post injury. No statistically significant differences were observed for complications (p=0.21).

Conclusion: Early decompression surgery following a SCI is safe and associated with higher AIS improvement at 6 mo following injury.

A New Classification of Thoracolumbar Injuries: The Importance of Injury Morphology, the Integrity of the Posterior Ligamentous Complex, and Neurological Status

Introduction: To devise a practical and comprehensive classification system to assist in clinical decision of operative or non-operative thoracolumbar injuries.

Methods/Population: Spine trauma specialists contributed factors that were deemed important for clinical decisions regarding thoracolumbar trauma. A new classification system called the Thoracolumbar Injury Classification and Severity Score (TLICS) was devised based on three parameters: 1) morphology of the injury determined radiographically, 2) integrity of posterior ligamentous complex, and 3) neurological status.

Conclusion: An easy to apply and clinically relevant decision making tool regarding thoracolumbar trauma.
• burst fracture (17%)
  ▪ stable: anterior and middle columns parted with bone retropulsed nearby
    ▪ hallmark is pedicle widening on AP x-ray
    ▪ spinal cord (seen on x-ray and CT); posterior column is uninjured
  ▪ unstable: same as the stable but with posterior column disruption (usually ligamentous)
• flexion distraction injury (6%)
  ▪ hyperflexion and distraction of posterior elements
  ▪ middle and posterior columns fail in distraction
  ▪ classic: Chance = horizontal fracture through posterior arch, pedicles, posterior vertebral body
  ▪ can be purely ligamentous, i.e. through PLL and disc
• fracture-dislocation (6%)
  ▪ anterior and cranial dislocation of superior vertebral body → 3 column failure
  ▪ three types:
    ▪ flexion-rotation
    ▪ flexion-distraction
    ▪ shear/hyperextension (rare)

Management of Thoracolumbar Injury
• severity and management based on TLICS classification

FRACTURES OF THE CERVICAL SPINE

Types of Injury
• C1 vertebral fracture (Jefferson fracture)
  ▪ vertical compression forces the occipital condyles of the skull down on the C1 vertebra (atlas), pushing the lateral masses of the atlas outward and disrupting the ring of the atlas
  ▪ also can cause an occipital condylar fracture
• odontoid process fracture
  ▪ causes C1 and odontoid of C2 to move independently of C2 body
  ▪ this occurs because
    ▪ normally C1 vertebra and odontoid of C2 are a single functional unit
    ▪ alar and transverse ligaments on posterior aspect of odontoid most commonly remain intact following injury
  ▪ patients often report a feeling of instability and present holding their head with their hands
• C2 vertebral fracture (hangman fracture, traumatic spondylolisthesis of axis):
  ▪ bilateral fracture through the pars interarticularis of C2 with subluxation of C2 on C3
  ▪ usually neurologically intact
• Clay-Shoveler fracture
  ▪ avulsion of spinous process, usually C6 or C7

Imaging
• AP spine x-ray (open-mouth and lateral view), CT

Treatment
• immobilization in cervical collar or halo vest until healing occurs (usually 2-3 mo)
• Type II and III odontoid fractures
  ▪ consider surgical fixation for comminution, displacement, or inability to maintain alignment with external immobilization
  ▪ confirm stability after recovery with flexion-extension x-rays

Neurologically Determined Death

Definition
• irreversible and diffuse brain injury resulting in absence of clinical brain function
• cardiovascular activity may persist for up to 2 wk

Criteria of Diagnosis
• prerequisites: no CNS depressant drugs/neuromuscular blocking agents, no drug intoxication/poisoning, temperature >32ºC, no electrolyte/acid-base/endocrine disturbance
• absent brainstem reflexes:
  ▪ absent pupillary light reflex
  ▪ absent corneal reflexes
  ▪ absent oculocephalic response
• absent caloric responses (e.g. no deviation of eyes to irrigation of each ear with 50 cc of ice water – allow 1 min after injection, 5 min between sides)
• absent pharyngeal and tracheal reflexes
• absent cough with tracheal suctioning
• absent respiratory drive at PaCO₂ >60 mmHg or >20 mmHg above baseline (apnea test)
• 2 evaluations separated by time, usually performed by two specialists (e.g. anesthetist, neurologist, neurosurgeon)
• confirmatory testing: flat EEG, absent perfusion assessed with cerebral angiogram

TLICS Scoring
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphology</td>
<td></td>
</tr>
<tr>
<td>Compression fracture</td>
<td>1</td>
</tr>
<tr>
<td>Burst fracture</td>
<td>2</td>
</tr>
<tr>
<td>Translational/rotational fracture</td>
<td>3</td>
</tr>
<tr>
<td>Distraction</td>
<td>4</td>
</tr>
<tr>
<td>Neurologic Status</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Nerve root injury</td>
<td>2</td>
</tr>
<tr>
<td>Spinal Cord Status</td>
<td></td>
</tr>
<tr>
<td>Incomplete</td>
<td>3</td>
</tr>
<tr>
<td>Complete</td>
<td>2</td>
</tr>
<tr>
<td>Cauda equine</td>
<td>3</td>
</tr>
<tr>
<td>Posterior Ligamentous Complex</td>
<td></td>
</tr>
<tr>
<td>Intact</td>
<td>0</td>
</tr>
<tr>
<td>Injury suspected/indeterminate</td>
<td>2</td>
</tr>
<tr>
<td>Injured</td>
<td>3</td>
</tr>
</tbody>
</table>

• TLICS scoring based on morphology of injury, status of posterior ligamentous complex, and neurological status
• Non-operative management if TLICS = 0-3, operative management if TLICS = 5+, either operative or non-operative if TLICS = 4
**Coma**

**Definition**
- an unrousable state in which patients show no meaningful response to environmental stimuli

**Pathophysiology**
- lesions affecting the cerebral cortex bilaterally, the reticular activating system (RAS) or their connecting fibres
- focal supratentorial lesions do not alter consciousness except by herniation (compression on the brainstem or on the contralateral hemisphere) or by precipitating seizures

**Classification**
- structural lesions (tumour, pus, blood, infarction, CSF): 1/3 of comas
  - supratentorial mass lesion: leads to herniation
  - infratentorial lesion: compression of or direct damage to the RAS or its projections
- metabolic disorders/diffuse hemispheric damage: 2/3 of comas
  - deficiency of essential substrates (e.g. oxygen, glucose, vitamin B₁₂)
  - exogenous toxins (e.g. drugs, heavy metals, solvents)
  - endogenous toxins/systemic metabolic diseases (e.g. uremia, hepatic encephalopathy, electrolyte imbalances, thyroid storm)
  - infections (meningitis, encephalitis)
  - trauma (concussion, diffuse shea axonal damage)

**Investigations and Management**
- ABCs
- labs: electrolytes, extended electrolytes, TSH, LFTs, Cr, BUN, toxin screen, glucose
- CT/MRI, LP, EEG

**Persistent Vegetative State**

**Definition**
- a condition of complete unawareness of the self and the environment accompanied by sleep-wake cycles with either complete or partial preservation of hypothalamic and brainstem autonomic function
- “awake but not aware”
- follows comatose state

**Etiology/Prognosis**
- most commonly caused by cardiac arrest or head injury
- due to irreversible loss of cerebral cortical function but intact brainstem function
- average life expectancy is 2-5 yr

**Pediatric Neurosurgery**

**Spinal Dysrampism**

**SPINA BIFIDA OCCULTA**

**Definition**
- congenital absence of a spinous process and a variable amount of lamina
- no visible exposure of meninges or neural tissue

**Epidemiology**
- 15-20% of the general population; most common at L5 or S1

**Etiology**
- failure of fusion of the posterior neural arch

**Clinical Features**
- no obvious clinical signs
- presence of lumbosacral cutaneous abnormalities (dimple, sinus, port-wine stain, or hair tuft) should increase suspicion of an underlying anomaly (lipoma, dermoid, diastematomyelia)

**Investigations**
- plain film: absence of the spinous process along with minor amounts of the neural arch
- U/S, MRI to exclude spinal anomalies

**Treatment**
- requires no treatment
MENINGOCELE (SPINA BIFIDA APERTA)

Definition
- herniation of meningeal tissue and CSF through a defect in the spine, without associated herniation of neural tissue

Etiology
- primary failure of neural tube closure

Clinical Features
- most common in lumbosacral area
- usually no disability, low incidence of associated anomalies, and hydrocephalus

Investigations
- plain films, CT, MRI, U/S, echo, GU investigations

Treatment
- surgical excision and tissue repair (excellent results)

MYELOMENINGOCELE (SPINA BIFIDA APERTA)

Definition
- herniation of meningeal and CNS tissue through a defect in the spine

Etiology
- same as meningocele

Clinical Features
- sensory and motor changes distal to anatomic level producing varying degrees of weakness
- urinary and fecal incontinence
- 65-85% of patients with myelomeningocele have hydrocephalus
- most have Type II Chiari malformation (see Chiari Malformations, NS36)

Investigations
- plain films, CT, MRI, U/S, echo, GU investigations

Treatment
- surgical closure to preserve neurologic status and prevent CNS infections
- closure in utero shown to decrease hydrocephalus and improve post natal motor scores

Prognosis
- operative mortality close to 0%, 95% 2-yr survival
- 80% have IQ >80 (but most are 80-95), 40-85% ambulatory, 3-10% have normal urinary continence
- early mortality usually due to Chiari malformation complications (respiratory arrest and aspiration), whereas late mortality is due to shunt malfunction

Intraventricular Hemorrhage

- see Pediatrics, P70

Hydrocephalus in Pediatrics

Etiology
- congenital
  - aqueductal anomalies, primary aqueductal stenosis in infancy
  - secondary gliosis due to intrauterine viral infections (mumps, varicella, TORCH)
  - Dandy-Walker malformation (2-4%)
  - Chiari malformation, especially Type II
  - myelomeningocele
- acquired
  - post meningitis
  - post hemorrhage (SAH, IVH)
  - masses (vascular malformation, neoplastic)

Clinical Features
- symptoms and signs of hydrocephalus are age related in pediatrics
- increased head circumference (HC), bulging anterior fontanelle, widened cranial sutures
- irritability, lethargy, poor feeding, and vomiting
- “cracked pot” sound on cranial percussion
- scalp vein dilation (increased collateral venous drainage)
- sunset sign – forced downward deviation of eyes
- episodic bradycardia and apnea
Investigations
- skull x-ray, U/S, CT, MRI, ICP monitoring

Treatment
- similar to adults (see Hydrocephalus, NS7)

Dandy-Walker Malformation

Definition
- atresia of foramina of Magendie and Luschka, resulting in:
  - complete or incomplete agenesis of the cerebellar vermis with widely separated, hypoplastic cerebellar hemispheres
  - posterior fossa cyst, enlarged posterior fossa
  - dilatation of 4th ventricle (also 3rd and lateral ventricles)
- associated anomalies
  - hydrocephalus (90%)
  - agenesis of corpus callosum (17%)
  - occipital encephalocele (7%)

Epidemiology
- 2-4% of pediatric hydrocephalus

Clinical Features
- 20% are asymptomatic, seizures occur in 15%
- symptoms and signs of hydrocephalus combined with a prominent occiput in infancy
- ataxia, spasticity, poor fine motor control common in childhood

Investigations
- ultrasound, CT, MRI

Treatment
- asymptomatic patients require no treatment
- associated hydrocephalus requires surgical treatment
  - e.g. ventriculoperitoneal (VP) shunt, cystoperitoneal (CP) shunt, lumboperitoneal (LP) shunt, ventriculoatrial (VA) shunt, lumbar drain

Prognosis
- 75-100% survival, 50% have normal IQ

Chiari Malformations

Definition
- malformations at the medullary-spinal junction

Etiology
- unclear, likely maldevelopment/dysgenesis during fetal life

Categories

Table 14. Categories of Chiari Malformations

<table>
<thead>
<tr>
<th></th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Cerebellar tonsils lie below the level of the foramen magnum</td>
<td>Part of cerebellar vermis, medulla, and 4th ventricle extend through</td>
</tr>
<tr>
<td></td>
<td></td>
<td>the foramen magnum often to midcervical region</td>
</tr>
<tr>
<td>Epidemiology</td>
<td>Average age at presentation 15 yr</td>
<td>Present in infancy</td>
</tr>
<tr>
<td>Clinical Features</td>
<td>Many are asymptomatic</td>
<td>Findings due to brainstem and lower cranial nerve dysfunction</td>
</tr>
<tr>
<td></td>
<td>Pain (69%), weakness (56%), numbness (52%), loss of temperature</td>
<td>Neurogenic dysphagia (59%), apnea (58%), stridor (56%), aspiration</td>
</tr>
<tr>
<td></td>
<td>sensation (40%)</td>
<td>(40%), arm weakness (27%), downbeat nystagmus</td>
</tr>
<tr>
<td></td>
<td>Central cord syndrome (65%)</td>
<td>Respiratory arrest is the most common cause of mortality</td>
</tr>
<tr>
<td></td>
<td>Foramen magnum compression syndrome (22%), Cerebellar syndrome (11%),</td>
<td>Usually associated with myelomingocele and hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Syringomyelia (50%), Hydrocephalus (10%)</td>
<td></td>
</tr>
<tr>
<td>Investigations</td>
<td>MRI</td>
<td>MRI</td>
</tr>
<tr>
<td>Treatment</td>
<td>Symptomatic patients (early surgery recommended, &lt;2 yr post symptom</td>
<td>Preserved</td>
</tr>
<tr>
<td></td>
<td>onset) suboccipital craniectomy, duraplasty</td>
<td>When symptomatic, check the shunt first. Then consider surgical</td>
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<td>decompression (which does not reverse intrinsic brainstem</td>
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<td>abnormalities)</td>
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<td></td>
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<td>cervical laminectomy, duraplasty</td>
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Figure 30. Chiari malformations
Craniosynostosis

Definition
• premature closure of the cranial suture(s)

Classification
• sagittal (most common): long narrow head with ridging sagittal suture (scaphocephaly)
• coronal: expansion in superior and lateral direction (brachiocephaly)
• metopic (trigonocephaly)
• lambdoid: least common

Epidemiology
• 0.6/1,000 live births, most cases are sporadic; familial incidence is 2% of sagittal and 8% of coronal synostosis

Clinical Features
• skull deformity, raised ICP ± hydrocephalus
• ophthalmologic problems due to increased ICP or bony abnormalities of the orbit
• must differentiate between positional plagiocephaly (secondary to back sleeping)

Investigations
• plain radiographs, CT scan

Treatment
• parental counseling about nature of deformity, associated neurological symptoms
• surgery for cosmetic purposes, except in cases of elevated ICP (≥2 sutures involved)

Pediatric Brain Tumours

• see Tumours, NS10

Epidemiology
• 20% of all pediatric cancers (second only to leukemia)
• 60% of pediatric brain tumours are infratentorial
• pediatric brain tumours arise from various cellular lineages
  • glia: low-grade astrocytoma (supra- or infratentorial), anaplastic astrocytoma, glioblastoma multiforme (largely supratentorial) (see Astrocytoma, NS12)
  • primitive nerve cells: supratentorial PNET
    • 90% of neonatal brain tumours, infratentorial (medulloblastoma), pineal gland (pineoblastoma)
  • non-neuronal cells: germ cell tumour, craniopharyngioma, dermoid, meningioma, neurinoma (schwannoma), pituitary adenoma, others

Clinical Features
• vomiting, seizure, macrocrania, hydrocephalus
• developmental delay, poor feeding, failure to thrive
• often initially escapes diagnosis due to expansile cranium and neural plasticity in children

Table 15. Overview of Childhood Primary Brain Tumours

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<th>Tumour Type</th>
<th>Characteristics</th>
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<tr>
<td>Pilocytic (low grade) Astrocytoma</td>
<td>Usually in posterior fossa, well circumscribed, benign, good prognosis</td>
</tr>
<tr>
<td>Medulloblastoma</td>
<td>A primitive neuroectodermal tumour (PNET), in cerebellum compresses 4th ventricle → hydrocephalus, highly malignant</td>
</tr>
<tr>
<td>Ependymoma</td>
<td>In 4th ventricle → hydrocephalus, poor prognosis</td>
</tr>
<tr>
<td>Hemangioblastoma</td>
<td>Often cerebellar, associated with von Hippel-Lindau syndrome with retinal angiomas, can produce EPO → secondary polycythemia</td>
</tr>
<tr>
<td>Craniopharyngioma</td>
<td>Causes bitemporal hemianopsia (thus often confused with pituitary adenoma), most common supratentorial childhood tumour, benign</td>
</tr>
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</table>
Functional Neurosurgery

Movement Disorders

- see Neurology, Tremor, Parkinson’s Disease, Dystonia, and Multiple Sclerosis, N32, N32, N34, N54, respectively

Table 16. Surgical Targets for Movement Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinson's Disease</td>
<td>Intractable contralateral bradykinesia/tremor Failure of medical management (advanced disease) Drug-induced dyskinesias (see dystonia, below)</td>
<td>Simultaneous, bilateral surgery/stimulation is most common Preferred target: anterodorsal thalamic nucleus (STN) Other targets: stereotactic ablation (pallidotomy)/stimulation of posteroventral globus pallidus pars interna (GPI) Caudal zona incerta Parkinsonian tremor: stereotactic ablation (thalamotomy)/stimulation of ventral intermediate (Vim) nucleus of thalamus</td>
<td>39-48% improvement in Unified Parkinson’s Disease Rating Scale (UPDRS) scores Reduced dosage of medications (STN) More effective than medical management in advanced PD Early intervention may reduce severity, course, and progression of disease Of little benefit for patients with atypical presentations</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias Involuntary movements Cognitive functioning: decreased lexical fluency, impaired executive function (STN &gt; GPi) Psychiatric: depression, mania, anxiety, apathy (STN &gt; GPi)</td>
</tr>
<tr>
<td>Dystonia</td>
<td>Contralateral primary (generalized) dystonias; cervical and tardive dystonias (GPI) Contralateral secondary dystonias (e.g. drug-induced: L-dopa, neuroleptics; STN)</td>
<td>Preferred target (primary dystonia): stereotactic ablation (pallidotomy)/stimulation of posteroventral GPi Secondary dystonia: stimulation of anterodorsal STN Stimulation of ventral posterior lateral (VPL) thalamic nucleus</td>
<td>Primary dystonia: 51% reduction in Burke-Fahn-Marsden Dystonia Scale (BFMDS) score Secondary dystonia: 62-89% improvement in dystonias Delayed effects: weeks → months</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%) Minor effects on cognitive functioning (especially decreased lexical fluency; STN &gt; GPi)</td>
</tr>
<tr>
<td>Tremor</td>
<td>Contralateral appendicular ET (first disorder to be treated by DBS; DBS is viable alternative to Rx) Intention tremor (IT) resulting from demyelination of cerebellar outflow tracts (e.g. in multiple sclerosis) Brainstem tremor (Holmes tremor)</td>
<td>Preferred target: stereotactic ablation (thalamotomy)/stimulation of Vim nucleus of thalamus Other targets: stimulation of caudal zona incerta Parkinsonian tremor: stimulation of anterodorsal STN</td>
<td>Durable reductions in essential tremor rating scale (ERTS) scores Reduced dosage of medications Conflicting data on vocal/facial tremor</td>
<td>Intracerebral hemorrhage, infection, seizure (1%-4%) Paresthesias/pain Dyssarthria Ataxia Minor effects on cognitive functioning (especially decreased lexical fluency) Tolerance may develop over time</td>
</tr>
</tbody>
</table>

Neuropsychiatric Disorders

- see Neurology, N35 and Psychiatry, PS17, PS9 for Tourette's Syndrome, Obsessive Compulsive Disorder and Depression

Table 17. Surgical Targets for Neuropsychiatric Disorders

<table>
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<th>Indications</th>
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<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obsessive Compulsive Disorder (OCD)</td>
<td>Severe symptoms refractory to medical management</td>
<td>Anterior capsulotomy/stimulation of the anterior limb of the internal capsule (IC)</td>
<td>Currently under investigation Reported 25-75% response rate</td>
<td>Intracerebral hemorrhages (1-2%) Mild effects on cognitive functioning Anxiety ± panic disorder (case report)</td>
</tr>
<tr>
<td>Tourette’s Syndrome</td>
<td>Severe symptoms refractory to medical management</td>
<td>Stimulation of midline intralaminar nuclei of the thalamus Stimulation of motor and limbic portions of GPi Stimulation of the anterior limb of the IC</td>
<td>Currently under investigation Reported &gt;70% reduction in vocal or motor tics + urge</td>
<td>Intracerebral hemorrhages (1-2%) Mild sexual dysfunction</td>
</tr>
<tr>
<td>Major Depressive Disorder (MDD)</td>
<td>Severe depression refractory to medical management and ECT</td>
<td>Stimulation of the subgenual cingulate cortex</td>
<td>Currently under investigation Reported 60% response rate; 35% remission rate</td>
<td>Intracerebral hemorrhages (1-2%) Pain, H/A Worsening mood, irritability</td>
</tr>
</tbody>
</table>
### Chronic Pain

#### Table 18. Surgical Targets for Chronic Pain

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Indications</th>
<th>Procedures</th>
<th>Outcomes</th>
<th>Morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neuropathic Pain</td>
<td>Severe, intractable, organic neuropathic pain (e.g. post-stroke pain, phantom limb pain, trigeminal neuralgia, chronic low-back pain, complex regional pain syndrome)</td>
<td>Preferred target: stimulation of the contralateral VPL VPM thalamic nuclei ± periventricular/periaqueductal grey matter (PVG/PAG) Other targets: stimulation of the contralateral IC Stimulation of the contralateral motor cortex</td>
<td>47% improvement in perception of pain intensity Less favourable results in central pain syndromes and poorly localized pain</td>
<td>Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder</td>
</tr>
<tr>
<td>Nociceptive Pain</td>
<td>Severe, intractable, organic nociceptive pain</td>
<td>Bilateral (most common) stimulation of the PVG/PAG</td>
<td>Reportedly 63% improvement in perception of pain intensity</td>
<td>Intracerebral hemorrhages (1-2%) Paresthesia Anxiety ± panic disorder</td>
</tr>
</tbody>
</table>

### Surgical Management of Epilepsy

- see Neurology, N18 for the medical treatment of epilepsy

#### Indications
- medically refractory seizures, usually defined as seizures resistant to two first line anti-seizure medications used in succession
- identification of a distinct epileptogenic region through clinical history, EEG, MRI, and neuropsychological testing; other localizing investigations include magnetoencephalography, SPECT, and PET
- if a distinct epileptogenic region cannot be identified, the patient may be a candidate for a palliative procedure such as corpus callosotomy

#### Procedure
- adults: resection of the hippocampus and parahippocampal gyrus for mesial temporal lobe epilepsy arising from mesial temporal sclerosis
- children: resection of an epileptogenic space-occupying lesion
- hemispherectomy and corpus callosotomy are less common

#### Outcomes
- 41-79% of adult patients are seizure free for 5 yr after temporal lobe resection
- 58-78% of children are seizure free after surgery
- surgery is associated with improvements in preexisting psychiatric conditions such as depression and anxiety, as well as improvement in quality of life measures

#### Morbidity
- 0.4-4% of surgical patients will have partial hemianopsia, aphasia, motor deficit, sensory deficit, or cranial nerve palsy following anteromedial temporal lobectomies
- most patients will have some decline in verbal memory following dominant temporal lobectomy and in visuospatial memory in non-dominant temporal resection
- the degree of memory decline stabilizes after 1-2 yr

#### Predictors
- positive predictive factors for seizure freedom following anteromedial temporal lobectomy
  - hippocampal sclerosis (unilateral)
  - focal localization of interictal epileptiform discharges
  - absence of pre-operative generalized seizures
  - tumoural cause
  - complete resection of the lesion

### Surgical Management for Trigeminal Neuralgia

- reserved for cases refractory to medical management; see Neurology, N44 for medical management

#### Surgical Options
- trigeminal nerve branch procedures
  - local blocks (phenol, alcohol)
  - neurectomy of the trigeminal branch

---

**A Randomized, Controlled Trial of Surgery for Temporal Lobe Epilepsy**
NEJM 2001;345:311-318

**Introduction:** This RCT evaluates the efficacy and safety of neurosurgery for temporal lobe epilepsy.

**Methods:** 80 patients with poorly controlled temporal lobe epilepsy were randomized for surgery (n=40) or for continued treatment with antiepileptic drugs (n=40). The primary outcome was freedom from seizures that impair awareness of self and surroundings during the period of 1 yr. Secondary outcomes included frequency and severity of seizures, quality of life, disability and death.

**Results:** The surgical group had higher cumulative proportion of patients without seizures impairing awareness compared to the medical group (p<0.01). The surgical group also had lower seizure frequency (p<0.001) and better quality of life (p<0.001). 4 patients in the surgical group had adverse effects (thalamic infarct, n=1; wound infection, n=1; verbal memory decline impairment occupation, n=2). One patient in the medical group died; no patients died in the surgical group.

**Conclusions:** In patients with poorly controlled temporal-lobe epilepsy, surgery is superior to prolonged medical therapy.
percutaneous trigeminal rhizotomy
microvascular decompression
radiofrequency thermocoagulation
Gamma Knife® radiosurgery
microvascular decompression
posterior fossa craniotomy with microsurgical exploration of the root entry zone, displacement of the vessel impinging on the nerve with placement of non-absorbable Teflon® felt

References


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## Obstetrics

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Basic Anatomy Review

FETAL CIRCULATION

Umbilical arteries (deoxygenated blood)
Umbilical vein (oxygenated blood)
Umbilical cord
Amnion
Chorion (fetal)
Decidua (maternal)
Endometrial artery
Endometrial vein
Placenta

MATERNAL CIRCULATION

Figure 1. Placental blood flow

Placenta
- site of fetal nutritive, respiratory, and excretory function
- discoid mass composed of fetal (chorion frondosum) and maternal (decidua basalis) tissues divided by tissues into cotyledons (lobules) on the uterine side
- produces hormones such as progesterone, placental lactogen, estrogen, relaxin, β-hCG, and IGFs
- poor implantation can lead to spontaneous abortion
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see Obstetrical Hemorrhage, OB14)

Pregnancy

Diagnosis of Pregnancy

History
- obstetrical and gynecological history
- obtain the year, location, mode of delivery, duration of labour, sex, gestational age, birth weight, and complications of every pregnancy; organize into GTPAL format
  - Gravidaity (G)
    - G: total number of pregnancies of any gestation (multiple gestation=one pregnancy)
    - includes current pregnancy, abortions, ectopic pregnancies, and hydattidiform moles
  - Parity (TPAL)
    - T: number of term infants delivered (>37 wk)
    - P: number of premature infants delivered (20-36+6 wk)
    - A: number of abortions (loss of intrauterine pregnancy prior to viability of fetus <20 wk and/or <500 g fetal weight)
      - induced (therapeutic) and spontaneous (miscarriage)
    - L: number of living children
- symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, and fatigue

Physical Signs
- Goodell’s sign: softening of the cervix (4-6 wk)
- Chadwick’s sign: bluish discolouration of the cervix and vagina due to pelvic vasculature engorgement (6 wk)
- Hegar’s sign: softening of the cervical isthmus (6-8 wk)
- uterine enlargement
- breast engorgement, areolae darkening, and prominent vascular patterns
- symptoms: amenorrhea, nausea and/or vomiting, breast tenderness, urinary frequency, and fatigue

Obstetric Hemorrhage
- abnormal location, implantation, or detachment can lead to antepartum hemorrhage (see Obstetrical Hemorrhage, OB14)

Acronyms

AC abdominal circumference
ACOG American Congress of Obstetricians and Gynecologists
AFI amniotic fluid index
AFP anteroposterior
AP anteroposterior
APS antiphospholipid antibody syndrome
BPP biophysical profile
CS Cesarean section
CGD cephalopheic disproportion
cardiotocography
CVS chorionic villus sampling
D&C dilatation and curettage
DIC disseminated intravascular coagulation
DVT deep vein thrombosis
ECV external cephalic version
EDC estimated date of confinement
EFM electronic fetal monitoring
EFW estimated fetal weight
FDP fibrin degradation products
FHR fetal heart rate
FSH fluorescence in situ hybridization
FL femur length
FM fetal movement
FPG fasting plasma glucose
FTS first trimester screen
GA gestational age
GBS Group B Streptococcus
GDM gestational diabetes mellitus
GTN gestational trophoblastic neoplasia
HC head circumference
HELPP hemolysis, elevated liver enzymes, low platelets
IGF infant growth factors
IMM intramyometrial
IOD induction of labour
IPS integrated prenatal screen
IUD intrauterine fetal death
IUGR intrauterine growth restriction
IVH intraventricular hemorrhage
L/S lecithin-sphingomyelin ratio
LLDP left lateral decubitus position
LMP last menstrual period
MSAFP maternal serum ß-fetoprotein
MSS maternal serum screen
MTX methotrexate
NPT non-invasive prenatal testing
NST non-stress test
NTDs neural tube defects
NTUS nuchal translucency ultrasound
OA occiput anterior
OGTT oral glucose tolerance test
ONTD open neural tube defect
OP decidua posterior
OT occult transverse
PAPP-A pregnancy-associated plasma protein a
PG plasma glucose
PPD postpartum depression
PPH postpartum hemorrhage
PPROM preterm premature rupture of membranes
PROM premature rupture of membranes
PITL preterm labour
RDS respiratory distress syndrome
ROM rupture of membranes
SFH symphysial fundal height
SOGC Society of Obstetricians and Gynaecologists of Canada
SVD spontaneous vaginal delivery
TENS transcutaneous electrical nerve stimulation
TPN total parenteral nutrition
UTI urinary tract infection
VBAC vaginal birth after Cesarean

Umbilical Vessels
- Always check the umbilical cord for 2 arteries and 1 vein: approximately 1/3 of babies with a single uterine artery will have another anomaly, IUGR or aneuploidy
Investigations
• β-hCG: peptide hormone composed of α and β subunits produced by placental trophoblastic cells – maintains the corpus luteum during pregnancy
  ▪ positive in serum 9 d post-conception, positive in urine 28 d after first day of LMP
  ▪ plasma levels double every 1-2 d, peak at 8-10 wk, then fall to a plateau until delivery
    • levels less than expected suggest: ectopic pregnancy, abortion, or inaccurate dates
    • levels greater than expected suggest: multiple gestation, molar pregnancy, Trisomy 21, or inaccurate dates
• U/S
  ▪ transvaginal
    • 5 wk amenorrhea: gestational sac visible
    • 6 wk: fetal pole visible
    • 7-8 wk: fetal heart activity visible
  ▪ transabdominal
    • 6-8 wk: intrauterine pregnancy visible (β-hCG ≥6,500 mIU/mL)

Maternal Physiologic Adaptations to Pregnancy

Table 1. Physiologic Changes During Pregnancy

| Skin | Increased pigmentation of perineum and areola, chloasma (pigmentation changes under eyes and on bridge of nose), linea nigra (midline abdominal pigmentation) Other: spider angiomas, palmar erythema due to increased estrogen, striae gravidarum due to connective tissue changes |
| Cardiovascular | Hyper-dynamic circulation  
Increased CO, HR, and blood volume  
Decreased blood pressure due to decreased PVR and decreased venous return from enlarging uterus compressing IVC and pelvic veins  
Increased venous pressure leads to risk of varicose veins, hemorrhoids, leg edema |
| Hematologic | Hemodilution causes physiologic anemia and apparent decrease in hemoglobin and hematocrit  
Increased leukocyte count but impaired function leads to improvement in autoimmune diseases  
Gestational thrombocytopenia: mild (platelets >70,000/µL) and asymptomatic, normalizes within 2-12 wk following delivery  
Hypercoagulable state: increased risk of DVT and PE but also decreased bleeding at delivery |
| Respiratory | Increased incidence of nasal congestion and epistaxis  
Increased O₂ consumption to meet increased metabolic requirements  
Elevated diaphragm (i.e. patient appears more "barrel-chested")  
Increased minute ventilation leads to decreased CO₂ resulting in mild respiratory alkalosis that helps CO₂ diffuse across the placenta from fetal to maternal circulation  
No change in VC and FEV₁  
Decreased TLC, FRC, and RV |
| Gastrointestinal | GERD due to increased intra-abdominal pressure and progesterone (causing decreased sphincter tone and delayed gastric emptying)  
Increased gallstones due to progesterone causing increased gallbladder stasis  
Constipation and hemorrhoids due to progesterone causing decreased GI motility |
| Genitourinary | Increased urinary frequency due to increased total urinary output  
Increased incidence of UTI and pyelonephritis due to urinary stasis (see Urinary Tract Infection, OB29)  
Glycosuria that can be physiologic especially in the 3rd trimester; must test for GDM  
Ureters and renal pelvis dilation (R>L) due to progesterone-induced smooth muscle relaxation and uterine enlargement  
Increased CO and thus increased GFR leads to decreased creatinine (normal in pregnancy 35-44 mmol/L), uric acid, and BUN |
| Neurologic | Increased incidence of carpal tunnel syndrome and Bell’s palsy |
| Endocrine | Thyroid: moderate enlargement and increased basal metabolic rate  
Increased total thyroxine and thyroxine binding globulin (TBG)  
Free thyroxine index and TSH levels are normal  
Adrenal: maternal cortisol rises throughout pregnancy (total and free)  
Calcium: decreased total maternal Ca²⁺ due to decreased albumin  
Free ionized Ca²⁺ (i.e. active) proportion remains the same due to parathyroid hormone (PTH), results in increased bone resorption and gut absorption, increased bone turnover (but no loss of bone density due to estrogen inhibition) |
**Antepartum Care**

- provided by obstetrician, family doctor, midwife, or multidisciplinary team (based on patient preference and risk factors)
- Antenatal Records (province specific)

### Preconception Counselling

- 3-8 wk GA is a critical period of organogenesis, so early preparation is vital
- **past medical history**: optimize illnesses and medications prior to pregnancy (see *Medical Complications of Pregnancy, OB26,* and *Medications in Pregnancy, OB11*)

#### supplementation
- folic acid: encourage diet rich in folic acid and supplement 8-12 wk preconception until end of T1 to prevent NTDs
  - 0.4-1 mg daily in all women; 5 mg if previous NTD, antiepileptic medications, DM, or BMI >35 kg/m²
- iron supplementation, prenatal vitamins

#### risk modification
- lifestyle: balanced nutrition and physical fitness
- medications: discuss teratogenicity of medications so they may be adjusted or stopped if necessary
- infection screening: rubella, HBsAg, VDRL, Pap smear, gonorrhea/chlamydia, HIV
- genetic testing as appropriate for high risk groups (see *Prenatal Screening, Table 2*); consider genetics referral in known carriers, recurrent pregnancy loss/stillbirth, family members with developmental delay or birth anomalies
- social: alcohol, smoking, street drugs, domestic violence (see *Family Medicine, FM11, FM13, FM27*)

### Initial Prenatal Visit

- usually within 8-12 wk of the first day of LMP or earlier if <20 or >35 yr old, bleeding, very nauseous, or other risk factors present
- Antenatal Records are filled out on the first prenatal visit

#### History
- gestational age by dates from the first day of the LMP
- if LMP unreliable, get a dating ultrasound which could coincide with nuchal translucency at ~12 wks
- dates should change if T1 U/S is greater than 5 days in difference from LMP due date
  - Naegle’s rule: 1st day of LMP + 7 d – 3 mo
  - e.g. LMP = 1 Apr 2014, EDC = 8 Jan 2015 (modify if cycle >28 d by adding number of d >28)
- history of present pregnancy (e.g. bleeding, N/V) and all previous pregnancies
- past medical, surgical, and gynecological history
- prescription and non-prescription medications
- family history: genetic diseases, birth defects, multiple gestation, consanguinity
- social history: smoking, alcohol, drug use, domestic violence (see *Family Medicine, FM11, FM13, FM27*)

#### Physical Exam
- complete physical exam to obtain baseline patient information
- BP and weight important for interpreting subsequent changes
- pelvic exam

#### Investigations
- blood work
  - CBC, blood group and Rh status, antibody screen, infection screening as per preconception counselling
- urine R&M, midstream urine C&S
  - screen for bacteriuria and proteinuria
- pelvic exam
  - Pap smear (only if required according to patient history and provincial screening guidelines), cervical or urine PCR for *N. gonorrhoeae* (GC) and *C. trachomatis*
Nausea and Vomiting

Epidemiology
• affects 50-90% of pregnant women
• often limited to T1 but may persist

Management
• rule out other causes of N/V
• weigh frequently, assess level of hydration, test urine for ketones
  • non-pharmacological
    ▪ avoid mixing fluids and solids, frequent small meals
    ▪ stop prenatal vitamins (folic acid must continue until >12 wk)
    ▪ increase sleep/rest
    ▪ ginger (maximum 1,000 mg/d)
    ▪ acupuncture, acupressure
  • pharmacological
    ▪ first line: Diclectin® (10 mg doxylamine succinate with vitamin B6) 4 tablets PO daily to maximum of 8 tablets
    ▪ if no improvement, try dimenhydrinate (50-100 mg q4-6h PO), followed by hydroxyzine, pyridoxine, phenothiazine, or metoclopramide
    ▪ vitamin B6 lollipops
    ▪ if patient dehydrated, assess fluid replacement needs and resuscitate accordingly
  • severe/refractory
    ▪ consider homecare with IV fluids and parenteral anti-emetics, hospitalization

Hyperemesis Gravidarum

Definition
• intractable N/V, usually presents in T1 then diminishes; occasionally persists throughout pregnancy
• affects ~1% of pregnancies

Etiology
• multifactorial with hormonal, immunologic, and psychologic components
• rapidly rising β-hCG ± estrogen levels may be implicated

Investigations
• rule out systemic causes: GI inflammation, pyelonephritis, thyrotoxicosis
• rule out obstetrical causes: multiple gestation, GTN, HELLP syndrome
• CBC, electrolytes, BUN, creatinine, LFTs, urinalysis
• ultrasound

Management
• thiamine supplementation may be indicated
• non-pharmacological (see Nausea and Vomiting, OB5)
• pharmacological options
  ▪ Diclectin® (for dosage, see Nausea and Vomiting, OB5)
  ▪ Dimenhydrinate can be safely used as an adjunct to Diclectin® (1 suppository bid or 25 mg PO qid)
  ▪ other adjuncts: hydroxyzine, pyridoxine, phenothiazine, metoclopramide
  ▪ also consider: ondansetron or methylprednisolone
  ▪ if severe: admit to hospital, NPO initially then small frequent meals, correct hypovolemia, electrolyte disturbance, and ketosis, TPN (if very severe) to reverse catabolic state

Complications
• maternal
  ▪ dehydration, electrolyte and acid-base disturbances
  ▪ Mallory-Weiss tear
  ▪ Wernicke's encephalopathy, if protracted course
  ▪ death
• fetal: usually none, IUGR is 15x more common in women losing >5% of pre-pregnancy weight
Subsequent Prenatal Visits

Timing
- for uncomplicated pregnancies, SOGC recommends q4-6wk until 30 wk, q2-3wk from 30 wk, and q1-2 from 36 wk until delivery

Assess at Every Visit
- estimated GA
- history: fetal movements, uterine bleeding, leaking, cramping, questions, concerns
- physical exam: BP, weight gain, SFH, Leopold's maneuvers (T3) for lie, position, and presentation of fetus
- investigations: urinalysis for glucosuria, proteinuria; fetal heart rate starting at 10-12 wk using Doppler U/S

Leopold's Maneuvers
- performed after 30-32 wk gestation
- first maneuver: to determine which fetal part is lying furthest away from the pelvic inlet
- second maneuver: to determine the location of the fetal back
- third maneuver: to determine which fetal part is lying above the pelvic inlet
- fourth maneuver: to locate the fetal brow

Small for Dates
- Date miscalculation
- IUGR
- Fetal demise
- Oligohydramnios

Large for Dates
- Date miscalculation
- Multiple gestation
- Polyhydramnios
- LGA (familial, DM)
- Fibroids

Prenatal Screening and Diagnostic Tests

Screening Tests
- testing should only occur following counselling and with the informed consent from the patient

Table 2. High-Risk Population Screening Tests

<table>
<thead>
<tr>
<th>Disease (Inheritance)</th>
<th>Population(s) at Risk</th>
<th>Screening Test(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia (AR)</td>
<td>Mediterranean, South East Asian, Western Pacific, African, Middle Eastern, Caribbean, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis, or HPLC</td>
</tr>
<tr>
<td>Sickle Cell (AR)</td>
<td>African, Caribbean, Mediterranean, Middle Eastern, Indian, South American</td>
<td>CBC (MCV and MCH), Hb electrophoresis, or HPLC</td>
</tr>
<tr>
<td>Cystic Fibrosis (CF) (AR)</td>
<td>Family history of CF in patient or partner or medical condition linked to CF like male infertility</td>
<td>CFTR gene DNA analysis</td>
</tr>
<tr>
<td>Tay Sachs Disease (AR)</td>
<td>Ashkenazi Jewish*, French Canadians, Cajun</td>
<td>Enzyme assay HEXA, or DNA analysis HEXA gene</td>
</tr>
<tr>
<td>Fragile X Syndrome (X-linked)</td>
<td>Family history – confirmed or suspected</td>
<td>DNA analysis: FMR-1 gene</td>
</tr>
</tbody>
</table>

AR = autosomal recessive; HEXA = hexosaminidase A; HPLC = high performance liquid chromatography
*If both partners are Ashkenazi Jewish, test for Canavan disease and Familial Dysautonomia (FD), if family history of a specific condition, look for carrier status: e.g. Gaucher, CF, Bloom syndrome, Niemann-Pick disease, etc. In all cases, if both partners positive, refer for genetic counselling.
### Table 3. Gestation-Dependent Screening Investigations

<table>
<thead>
<tr>
<th>Gestational Age (wk)</th>
<th>Investigations</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>8-12</td>
<td>Dating U/S, possible Pap smear, chlamydia/gonorrhea cultures, urine C&amp;S, HIV, VDRL, HepB5Ag, Parovirus IgM or IgG if high risk (small child at home or daycare worker/primary teacher), Varicella IgG if no history of disease/immunization, CBC, blood group and screen</td>
<td></td>
</tr>
<tr>
<td>10-12</td>
<td>CVS</td>
<td>Measures 1. Nuchal translucency on U/S 2. β-hCG 3. PAPP-A</td>
</tr>
<tr>
<td>11-14</td>
<td>FTS IPS Part 1</td>
<td>Measures 1. Nuchal translucency on U/S 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>11-14</td>
<td>Nuchal translucency U/S</td>
<td>Measures 1. Nuchal translucency on U/S 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>15-16 to term</td>
<td>Amniocentesis</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>15-20</td>
<td>IPS Part 2 (or MSAFP only for patients who did FTS earlier)</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>18-20 to term</td>
<td>Fetal movements (quickening)</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>18-20</td>
<td>U/S for dates, fetal growth, and anatomy assessment</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>24-28</td>
<td>Gestational Diabetes Screen 50 g OGCT</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>28</td>
<td>Repeat CBC</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
<tr>
<td>35-37</td>
<td>GBS screen</td>
<td>Measures 1. MSAFP 2. β-hCG 3. Unconjugated estrogen (estriol or µE3) 4. Inhibin A</td>
</tr>
</tbody>
</table>

Maternal serum screen is also referred to as Triple Screen; if Inhibin A is also tested, it is referred to as Quadruple Screen. Ideally testing for MSS and IPS Part 2 occur between 15-18 wk to give women more time to make decisions and move ahead with diagnostic testing should the resulting screen be positive.

### Ultrasound Screening
- **8-12 wk GA**: Dating Ultrasound (most accurate form of pregnancy dating)
  - measurement of crown-rump length (margin of error ± 5 d)
  - change EDC to U/S date if >5 d discrepancy from EDC based on LMP
- **11-14 wk GA**: NTUS
  - measures the amount of fluid behind the neck of the fetus
  - early screen for Trisomy 21 (may also detect cardiac and other aneuploidies like Turner’s syndrome)
  - NT measurement is necessary for the FTS and IPS Part 1
- **18-20 wk GA**: Growth and Anatomy U/S (margin of error ± 10 d)
  - earlier or subsequent ultrasounds performed when medically indicated

### Non-Invasive Prenatal Testing (NIPT)
- non-invasive screening for Down syndrome and other chromosomal abnormalities in spontaneous singleton pregnancies
- analyses maternal blood for circulating cell free fetal DNA (ccffDNA) at 10 wk GA

### Advantages
- high sensitivity (98-99%), FP<2%

### Disadvantages
- less sensitive for Trisomy 18 and 13
- low specificity (all positive results must be confirmed with amniocentesis)
- does not screen for oNTD
Diagnostic Tests

Indications
- age >35 yr (increased risk of chromosomal anomalies)
- risk factors in current pregnancy
  - abnormal U/S
  - abnormal prenatal screen (IPS, FTS, or MSS)
- past history/family history of
  - previous pregnancy or family history of chromosomal anomaly or genetic disease
  - either parent a known carrier of a genetic disorder or balanced translocation
  - consanguinity
  - >3 spontaneous abortions

AMNIOCENTESIS
- U/S-guided transabdominal extraction of amniotic fluid

Indications
- identification of genetic anomalies (15-16 wk gestation) as per indications above
- confirmation of positive NIPT testing
- positive FTS/IPS
- assessment of fetal lung maturity (T3) via the L/S ratio (lecithin:sphingomyelin)
  - if >2:1, RDS is less likely to occur

Advantages
- also screens for oNTD (acetylcholinesterase and amniotic AFP) – 96% accurate
- in women >35 yr, the risk of chromosomal anomaly (1/180) is greater than the risk of miscarriage from the procedure
- more accurate genetic testing than CVS

Disadvantages
- 1/400-1/500 risk of spontaneous abortion
- results take 14-28 d; FISH can be done on chromosomes X, Y, 21, 13, 18 to give preliminary results in 48 h

CHORIONIC VILLUS SAMPLING
- biopsy of fetal-derived chorion using a transabdominal needle or transcervical catheter at 10-12 wk

Advantages
- enables pregnancy to be terminated earlier than with amniocentesis
- rapid karyotyping and biochemical assay within 48 h, including FISH analysis
- high sensitivity and specificity

Disadvantages
- 1-2% risk of spontaneous abortion
- does not screen for oNTD
- 1-2% incidence of genetic mosaicism “false negative” results

Table 4. Comparison of FTS, MSS, and IPS

<table>
<thead>
<tr>
<th>FTS</th>
<th>MSS</th>
<th>IPS</th>
</tr>
</thead>
<tbody>
<tr>
<td>11-14 wk</td>
<td>15-20 wk</td>
<td>11-13 wk U/S-Nuchal Translucency</td>
</tr>
<tr>
<td>Risk estimate for 1. Down syndrome (Trisomy 21): increased NT, increased ( \beta )-hCG</td>
<td>Risk estimate for 1. oNTD: increased MSAFP (sensitivity 80-90%)</td>
<td>Risk estimate for 1. oNTD, Trisomy 21, Trisomy 18</td>
</tr>
<tr>
<td>2. Trisomy 18: increased NT, decreased PAPP-A, decreased ( \beta )-hCG</td>
<td>2. Trisomy 21: decreased MSAFP, increased ( \beta )-hCG, decreased ( \mu )E3 (sensitivity 65%)</td>
<td>Sensitivity ~85-90%</td>
</tr>
<tr>
<td>Note: does not measure risk of open neural tube defect (oNTD) and should be combined with MSAFP at 11-13 wk</td>
<td>3. Trisomy 18: decreased MSAFP, decreased ( \beta )-hCG, decreased ( \mu )E3, decreased inhibin (sensitivity 80%)</td>
<td>2% false positive rate</td>
</tr>
<tr>
<td>More accurate estimate of Down syndrome risk than MSS, sensitivity ~85% (when combined with age)</td>
<td>Only offered alone if patient missed the time window for IPS or FTS</td>
<td>Patients with positive screen should be offered U/S, amniocentesis, or NIPT (covered in some provinces, self-pay in others)</td>
</tr>
<tr>
<td>5% false positive rate</td>
<td>8% baseline false positive rate for Trisomy 21, lower for oNTD and Trisomy 18</td>
<td></td>
</tr>
<tr>
<td>Patients with positive screen should be offered CVS, amniocentesis, or NIPT (covered in some provinces, self-pay in others)</td>
<td>Patients with positive screen should be offered U/S, amniocentesis, or NIPT (covered in some provinces, self-pay in others)</td>
<td></td>
</tr>
</tbody>
</table>

Note: In twins, FTS, MSS, and IPS are not applicable; screen with NT for chromosomal abnormalities and MSAFP for oNTDs

Compared to CVS, amniocentesis has a higher accuracy of prenatal cytogenetic diagnosis (99.8% vs. 97.5%) and lower risk of spontaneous abortion (0.5% vs. 1-2%)

Risk Factors for Neural Tube Defects

GRIMM
- Genetics: family history of NTD (risk of having second child with NTD is increased to 2-5%), consanguinity, chromosomal (characteristic of Trisomy 13, 18, and 21)
- Race: European Caucasians > African Americans, 3-fold higher in Hispanics
- Insufficient vitamins: zinc and folate
- Maternal chronic disease (e.g. DM)
- Maternal use of antiepileptic drugs
- General population risk for NTD is 0.1%
ISOIMMUNIZATION SCREENING

Definition
• isoimmunization: antibodies (Ab) produced against a specific RBC antigen (Ag) as a result of antigenic stimulation with RBC of another individual

Etiology
• maternal-fetal circulation normally separated by placental barrier, but sensitization can occur and can affect the current pregnancy, or more commonly, future pregnancies
• Anti-Rh Ab produced by a sensitized Rh-negative mother can lead to fetal hemolytic anemia
• Risk of isoimmunization of an Rh-negative mother with an Rh-positive ABO-compatible infant is 16%
• sensitization routes
  • incompatible blood transfusions
  • previous fetal-maternal transplacental hemorrhage (e.g. ectopic pregnancy, abruption)
  • invasive procedures in pregnancy (e.g. prenatal diagnosis, cerclage, D&C)
  • any type of abortion
  • labour and delivery

Investigations
• Screening with indirect Coombs test at first visit for blood group, Rh status, and antibodies
• Kleihauer-Betke test used to determine extent of fetomaternal hemorrhage by estimating volume of fetal blood volume that entered maternal circulation
• detailed U/S for hydrops fetalis

Prophylaxis
• exogenous Rh IgG (Rhogam® or WinRho®) binds to Rh antigens of fetal cells and prevents them from contacting maternal immune system
• Rhogam® (300 µg) given to all Rh negative and antibody screen negative women in the following scenarios
  ▪ routinely at 28 wk GA (provides protection for ~12 wk)
  ▪ within 72 h of the birth of an Rh positive fetus
  ▪ with a positive Kleihauer-Betke test
  ▪ with any invasive procedure in pregnancy (CVS, amniocentesis)
  ▪ in ectopic pregnancy
  ▪ with miscarriage or therapeutic abortion
  ▪ with an antepartum hemorrhage
• if Rh negative and Ab screen positive, follow mother with serial monthly Ab titres throughout pregnancy ± serial amniocentesis as needed (Rhogam® has no benefit)

Investigations
• MCA dopplers are done to assess degree of fetal anemia or if not available bilirubin is measured by serial amniocentesis to assess the severity of hemolysis
• cordocentesis for fetal Hb should be used cautiously (not first line)

Treatment
• falling biliary pigment warrants no intervention (usually indicative of either unaffected or mildly affected fetus)
• intrauterine transfusion of O-negative pRBCs may be required for severely affected fetus or early delivery of the fetus for exchange transfusion

Complications
• anti-Rh IgG can cross the placenta and cause fetal RBC hemolysis resulting in fetal anemia, CHF, edema, ascites
• severe cases can lead to fetal hydrops (edema in at least two fetal compartments due to fetal heart failure secondary to anemia) or erythroblastosis fetalis (moderate to severe immune-mediated hemolytic anemia)
Counselling of the Pregnant Woman

Nutrition

- Canada’s Food Guide to Healthy Eating suggests
  - 3-4 servings of milk products daily (greater if multiple gestation)
  - a daily caloric increase of ~100 cal/d in the 1st trimester, ~300 cal/d in the second and third trimesters and ~450 cal/d during lactation
  - daily multivitamin should be continued in the 2nd trimester for women who do not consume an adequate diet; otherwise routine vitamin supplementation is not necessary (avoid excess vitamin A)
- nutrients important during pregnancy
  - folate: 0.4 mg/d for first 12 wk (5 mg/d if high risk)
  - supports increase in blood volume, growth of maternal and fetal tissue, decreases incidence of NTD
  - foods rich in folic acid include: spinach, lentils, chick peas, asparagus, broccoli, peas, brussels sprouts, corn, and oranges
  - calcium: 1200-1500 mg/d
  - maintains integrity of maternal bones, skeletal development of fetus, breast milk production
  - vitamin D: 1,000 IU
  - promotes calcium absorption
  - iron: 0.8 mg/d in T1, 4-5 mg/d in T2, and >6 mg/d in T3
  - supports maternal increase in blood cell mass, supports fetal and placental tissue
  - required amounts exceed normal body stores and typical intake, and therefore need supplemental iron
  - iron is the only known nutrient for which requirements during pregnancy cannot be met by diet alone (see Iron Deficiency Anemia, OB26)
  - essential fatty acids – supports fetal neural and visual development
  - contained in vegetable oils, margarines, peanuts, fatty fish

Caffeine

- diuretic and stimulant that readily crosses placenta
- less than 300 mg/d is not thought to contribute to miscarriage or preterm birth (ACOG)
- relationship between caffeine and IUGR is unknown (ACOG)
- SOGC states 1-2 cups/d are safe during pregnancy

Herbal Teas and Preparations

- not enough scientific information about safety of various herbs and herbal products to recommend their use during pregnancy
- some herbal teas can have toxic or pharmacological effects on the mother or fetus
- chamomiles have been reported to exhibit adverse effects on the uterus

Foodborne Illnesses

- microbiological contamination of food may occur through cross-contamination and/or improper food handling
  - listeriosis (*Listeria monocytogenes*) and toxoplasmosis (*Toxoplasma gondii*) are of concern during pregnancy
  - avoid consumption of raw meats, fish, poultry, raw eggs, and unpasteurized dairy products
  - avoid unpasteurized soft cheeses, deli meats, smoked salmon, and pates as they may be sources of *Listeria*
  - chemical contamination of food
  - current guideline for mercury of 0.5 ppm in fish is not considered harmful for the general population, including pregnant women
  - Health Canada advises pregnant women to limit consumption of top predator fish such as shark, swordfish, king mackerel, tilefish

Lifestyle

- exercise under physician guidance
- absolute contraindications
  - ruptured membranes, preterm labour, hypertensive disorders of pregnancy, incompetent cervix, IUGR, multiple gestations (>3), placenta previa after 28th wk, persistent 2nd or 3rd trimester bleeding, uncontrolled type I DM, uncontrolled thyroid disease, or other serious cardiovascular, respiratory, or systemic disorder
• relative contraindications
  • previous preterm birth, mild/moderate cardiovascular or respiratory disorder, anemia (Hb ≤10 g/dL), malnutrition or eating disorder, twin pregnancy after 28th wk, other significant medical conditions
• weight gain: optimal gain depends on pre-pregnancy BMI (varies from 6.8-18.2 kg)
• work: strenuous work, extended hours and shift work during pregnancy may be associated with greater risk of low birth weight, prematurity, and spontaneous abortion
• air travel is acceptable in second trimester; airline cut off for travel is 36-38 wk gestation depending on the airline to avoid giving birth on the plane
• sexual intercourse: may continue, except in patients at risk for: abortion, preterm labour, or placenta previa; breast stimulation may induce uterine activity and is discouraged in high-risk patients near term
• smoking: assist/encourage to reduce or quit smoking
  • increased risk of decreased birth weight, placenta previa/abruption, spontaneous abortion, preterm labour, stillbirth
• alcohol: no amount of alcohol is safe in pregnancy; encourage abstinence from alcohol during pregnancy; alcohol increases incidence of abortion, stillbirth, and congenital anomalies
  • fetal alcohol syndrome (see Pediatrics, P25)
• cocaine: microcephaly, growth retardation, prematurity, abruptio placenta

Medications

• most drugs cross the placenta to some extent
• very few drugs are teratogenic, but very few drugs have proven safety in pregnancy
• use any drug with caution and only if necessary
• analgesics: acetaminophen preferable to ASA or ibuprofen

Table 5. Documented Adverse Effects, Contraindicated

<table>
<thead>
<tr>
<th>Contraindicated Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEI</td>
<td>Fetal renal defects, IUGR, oligohydramnios</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Stains infant’s teeth, may affect long bone development</td>
</tr>
<tr>
<td>Retinoids (e.g. Accutane®)</td>
<td>CNS, craniofacial, cardiac, and thymic anomalies</td>
</tr>
<tr>
<td>Misoprostol</td>
<td>Mobius syndrome (congenital facial paralysis with or without limb defects, spontaneous abortion, preterm labour)</td>
</tr>
</tbody>
</table>

Table 6. Documented Adverse Effects, Weigh Benefits vs. Risks, and Consider Medication Change

<table>
<thead>
<tr>
<th>Medication</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Fetal hydantoin syndrome in 5-10% (IUGR, mental retardation, facial dysmorpheogenesis, congenital anomalies)</td>
</tr>
<tr>
<td>Valproate</td>
<td>oNTD in 1%</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>oNTD in 1-2%</td>
</tr>
<tr>
<td>Lithium</td>
<td>Ebstein's cardiac anomaly, goitre, hypotension</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Increased incidence of spontaneous abortion, stillbirth, prematurity, IUGR, fetal warfarin syndrome (nasal hypoplasia, epiphyseal stippling, optic atrophy, mental retardation, intracranial hemorrhage)</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Maternal liver damage (acute fatty liver)</td>
</tr>
<tr>
<td>Sulpha drugs</td>
<td>Anti-folate properties, therefore theoretical risk in T1; risk of kernicterus in T3</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>Grey baby syndrome (fetal circulatory collapse 2° to toxic accumulation)</td>
</tr>
</tbody>
</table>

Immunizations

Intrapartum

• administration is dependent on the risk of infection vs. risk of immunization complications
• safe: tetanus toxoid, diphtheria, influenza, hepatitis B, pertussis
• avoid live vaccines (risk of placental and fetal infection): polio, measles/mumps/rubella, varicella
• contraindicated: oral typhoid

Postpartum

• rubella vaccine for all non-immune mothers
• hepatitis B vaccine should be given to infant within 12 h of birth if maternal status unknown or positive – follow-up doses at 1 and 6 mo
• human papillomavirus (HPV) vaccine – if meets criteria
• safe: tetanus toxoid, diphtheria, influenza, hepatitis B, pertussis, varicella
Radiation

- ionizing radiation exposure is considered teratogenic at high doses
  - if indicated for maternal health, should be done
- imaging not involving direct abdominal/pelvic high dosage is not associated with adverse effects
  - higher dosage to fetus: plain x-ray of lumbar spine/abdomen/pelvis, barium enema, CT abdomen, pelvis, lumbar spine
- most investigations involve minimal radiation exposure
- radioactive isotopes of iodine are contraindicated
- no known adverse effects from Ultrasound or MRI (long-term effects of gadolinium unknown, avoid if possible)

Table 7. Approximate Fetal Doses from Common Diagnostic Procedures

<table>
<thead>
<tr>
<th>Examination</th>
<th>Estimated Fetal Dose (rad)</th>
<th>Number of Exams Safe in Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain Film</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-14</td>
<td>35</td>
</tr>
<tr>
<td>Pelvis</td>
<td>0-11</td>
<td>45</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0-17</td>
<td>29</td>
</tr>
<tr>
<td>Thoracic spine</td>
<td>0.009</td>
<td>555</td>
</tr>
<tr>
<td>Chest (2 views)</td>
<td>&lt;0.001</td>
<td>5000</td>
</tr>
<tr>
<td>CT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdomen</td>
<td>0-8</td>
<td>6</td>
</tr>
<tr>
<td>Pelvis</td>
<td>2-5</td>
<td>2</td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>0-24</td>
<td>20</td>
</tr>
<tr>
<td>Chest</td>
<td>0.006</td>
<td>833</td>
</tr>
</tbody>
</table>


Antenatal Fetal Surveillance

Fetal Movements

- patients will generally first notice fetal movement ("quickening") at 18-20 wk in primigravidas; can occur 1-2 wk earlier in multigravidas; can occur 1-2 wk later if placenta is implanted on the anterior wall of uterus
- if the patient is concerned about decreased fetal movement, she is counselled to choose a time when the fetus is normally active to count movements (usually recommended after 26 wk)
- all high risk women should be told to do FM counts
  - if there is a subjective decrease in fetal movement, try drinking juice, eating, changing position, or moving to a quiet room and count for 2 h; ≥6 movements in 2 h expected
  - if there are <6 movement counts in 2 h, patient should present to labour and delivery triage

NON-STRESS TEST

Definition
- FHR tracing ≥20 min using an external Doppler to assess FHR and its relationship to fetal movement (see Fetal Monitoring in Labour, OB35)

Indication
- any suggestion of uteroplacental insufficiency or suspected compromise in fetal well-being
Table 8. Classification of Antepartum Non-Stress Test

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal NST (Previously “Reactive”)</th>
<th>Atypical NST (Previously “Non-Reactive”)</th>
<th>Abnormal NST (Previously “Non-Reactive”)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>110-160 bpm</td>
<td>100-110 bpm or &gt;160 bpm for &lt;30 min</td>
<td>Bradycardia &lt;100 bpm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rising baseline</td>
<td>Tachycardia &gt;160 for &gt;30 min</td>
</tr>
<tr>
<td>Variability</td>
<td>6-25 bpm (moderate) ≤5 (absent or minimal) for &lt;40 min</td>
<td>5 (absent or minimal) for 40-80 min</td>
<td>≤5 for 80 min Sinusoidal 25 bpm for &gt;10 min</td>
</tr>
<tr>
<td>Decelerations</td>
<td>None or occasional variable &lt;30 s</td>
<td>Variable decelerations 30-60 s duration</td>
<td>Variable decelerations &gt;60 s Late deceleration(s)</td>
</tr>
<tr>
<td>Accelerations in Term Fetus</td>
<td>2 accelerations with acme of ≥15 bpm, lasting 15 s over &lt;40 min of testing</td>
<td>2 accelerations with acme of ≥15 bpm, lasting 15 s in 40-90 min</td>
<td>&lt;2 accelerations with acme of ≥15 bpm, lasting 15 s in &gt;80 min</td>
</tr>
<tr>
<td>Accelerations in Preterm Fetus (≤32 wk)</td>
<td>&gt;2 accelerations with acme of &gt;10 bpm, lasting 10 s in &lt;40 min</td>
<td>&lt;2 accelerations with acme of &gt;10 bpm, lasting 10 s in 40-90 min</td>
<td>&lt;2 accelerations with acme of &gt;10 bpm, lasting 10 s in &gt;80 min</td>
</tr>
<tr>
<td>Action</td>
<td>FURTHER ASSESSMENT OPTIONAL, based on total clinical picture</td>
<td>FURTHER ASSESSMENT REQUIRED</td>
<td>URGENT ACTION REQUIRED An overall assessment of the situation and further investigation with U/S or BPP is required; some situations will require delivery</td>
</tr>
</tbody>
</table>

Adapted from: SOGC, Fetal Health Surveillance: Antepartum and Intrapartum Consensus Guideline, September 2007

Operating Characteristics
- false positive rate depends on duration; false negative rate = 0.2-0.3%

Interpretation
- normal: at least 2 accelerations of FHR >15 bpm from the baseline lasting >15 s, in 20 min
- abnormal: <2 accelerations of FHR in 40 min
- if no observed accelerations or fetal movement in the first 20 min, stimulate fetus (fundal pressure, acoustic/vibratory stimulation) and continue monitoring for 30 min
- if NST abnormal, then perform BPP

BIOPHYSICAL PROFILE

Definition
- U/S assessment of the fetus ± NST

Indications
- abnormal or atypical NST
- post-term pregnancy
- decreased fetal movement
- IUGR
- any other suggestion of fetal distress or uteroplacental insufficiency

Operating Characteristics
- false positive rate ≤30%, false negative rate = 0.1%

Table 9. Scoring of the BPP

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reassuring (2 points)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb Extension then Flexion</td>
<td>At least one episode of limb extension followed by flexion</td>
</tr>
<tr>
<td>AFV*</td>
<td>Fluid pocket of 2 cm in 2 axes</td>
</tr>
<tr>
<td>Movement</td>
<td>Three discrete movements</td>
</tr>
<tr>
<td>Breathing</td>
<td>At least one episode of breathing lasting at least 30 s</td>
</tr>
</tbody>
</table>

*AFV is a marker of chronic hypoxia; all other parameters indicate acute hypoxia

Interpretation
- 8: perinatal mortality rate 1:1,000; repeat BPP as clinically indicated
- 6: perinatal mortality 31:1,000; repeat BPP in 24 h
- 0-4: perinatal mortality rate 200:1,000; deliver fetus if benefits of delivery outweigh risks
### Obstetrical Hemorrhage

**Definition**
- vaginal bleeding from 20 wk to term

**Differential Diagnosis**
- bloody show (shedding of cervical mucus plug) – most common etiology in T3
- placenta previa
- abruptio placenta – most common pathological etiology in T3
- vasa previa
- cervical lesion (cervicitis, polyp, ectropion, cervical cancer)
- uterine rupture
- other: bleeding from bowel or bladder, placenta accreta, abnormal coagulation

**Table 10. Comparison of Placenta Previa vs. Abruptio Placentae**

<table>
<thead>
<tr>
<th></th>
<th>Placenta Previa</th>
<th>Abruptio Placentae</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Abnormal location of the placenta near, partially, or completely over the internal cervical os</td>
<td>Premature separation of a normally implanted placenta after 20 wk GA</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Idiopathic</td>
<td>Idiopathic</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>0.5-0.8% of all pregnancies</td>
<td>1-2% of all pregnancies</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>• History of placenta previa (4-8% recurrence risk)</td>
<td>• Previous abruption (recurrence rate 5-16%)</td>
</tr>
<tr>
<td></td>
<td>• Multiparity</td>
<td>• Maternal HTN (chronic or gestational HTN in 50% of abruptions) or vascular disease</td>
</tr>
<tr>
<td></td>
<td>• Increased maternal age</td>
<td>• Cigarette smoking (&gt;1 pack/d), excessive alcohol consumption, cocaine</td>
</tr>
<tr>
<td></td>
<td>• Multiple gestation</td>
<td>• Multiparity and/or maternal age &gt; 35 yr</td>
</tr>
<tr>
<td></td>
<td>• Uterine tumour (e.g. fibroids) or other uterine anomalies</td>
<td>• PPROM</td>
</tr>
<tr>
<td></td>
<td>• Uterine scar due to previous abortion, C/S, D&amp;C, myomectomy</td>
<td>• Rapid decompression of a distended uterus (polyhydramnios, multiple gestation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Uterine anomaly, fibroids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Trauma (e.g. motor vehicle collision, maternal battery)</td>
</tr>
<tr>
<td><strong>Bleeding</strong></td>
<td>PAINLESS</td>
<td>Usually PAINFUL</td>
</tr>
</tbody>
</table>

### Placenta Previa

**Definition**
- placenta implanted in the lower segment of the uterus, presenting ahead of the leading pole of the fetus
- the distance of the placental edge from the internal os is described in “millimetres away” from the internal os or “millimetres of overlap” over the internal os
- greater than 20 millimetres of overlap over the internal os in the third trimester of pregnancy is highly predictive of the need for a C/S
- any degree of overlap after 35 wk is an indication for a C/S

**Clinical Features**
- PAINLESS bright red vaginal bleeding (recurrent), may be minimized and cease spontaneously, but can become catastrophic
- mean onset of bleeding is 30 wk GA, but onset depends on degree of previa
- physical exam
  - uterus soft and non-tender
  - presenting fetal part high or displaced
  - FHR usually normal
  - shock/anemia correspond to degree of apparent blood loss
- complications
  - fetal
    - perinatal mortality low but still higher than with a normal pregnancy
    - prematurity (bleeding often dictates early C/S)
    - intrauterine hypoxia (acute or IUGR)
    - fetal malpresentation
    - PPROM
    - risk of fetal blood loss from placenta, especially if incised during C/S
  - maternal
    - <1% maternal mortality
    - hemorrhage and hypovolemic shock, anemia, acute renal failure, pituitary necrosis (Sheehan syndrome)
    - placenta accreta – especially if previous uterine surgery, anterior placenta previa
    - hysterectomy
Investigations
• transvaginal U/S is more accurate than transabdominal U/S at diagnosing placenta previa at any gestational age
• if the placenta lies between 20 mm of overlap and 20 mm away from the internal os after 20 wk, transvaginal ultrasounds should be repeated in the third trimester as continued change in the placental location is likely

Management
• goal: keep pregnancy intrauterine until the risk of delivery < risk of continuing pregnancy
• stabilize and monitor
  ▪ maternal stabilization: large bore IV with hydration, O2 for hypotensive patients
  ▪ maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, INR/PTT, platelets, fibrinogen, FDP, type and cross match)
  ▪ electronic fetal monitoring
  ▪ U/S assessment: when fetal and maternal condition permit, determine fetal viability, gestational age, and placental status/position
• Rhogam® if mother is Rh negative
  ▪ Kleihauer-Betke test to determine extent of fetomaternal transfusion so that appropriate dose of Rhogam® can be given
• GA <37 wk and minimal bleeding: expectant management
  ▪ admit to hospital
  ▪ limited physical activity, no douches, enemas, or sexual intercourse
  ▪ consider corticosteroids for fetal lung maturity
• delivery when fetus is mature or hemorrhage dictates
• GA ≥37 wk, profuse bleeding, or L/S ratio is >2:1 – deliver by C/S

Abruptio Placentae
Clinical Features
• classification
  ▪ total (fetal death inevitable) vs. partial
  ▪ external/revealed/apparent: blood dissects downward toward cervix
  ▪ internal/concealed (20%): blood dissects upward toward fetus
  ▪ most are mixed
• presentation
  ▪ usually PAINFUL (80%) vaginal bleeding (bleeding not always present if abruption is concealed), uterine tenderness, uterine contractions
  ▪ pain: sudden onset, constant, localized to lower back and uterus
  ▪ shock/anemia out of proportion to apparent blood loss
  ▪ ± fetal distress, fetal demise (15% present with demise), bloody amniotic fluid (fetal presentation typically normal)
  ▪ ± coagulopathy

Complications
• fetal complications: perinatal mortality 25-60%, prematurity, intrauterine hypoxia
• maternal complications: <1% maternal mortality, DIC (in 20% of abruptions), acute renal failure, anemia, hemorrhagic shock, pituitary necrosis (Sheehan syndrome), amniotic fluid embolus

Investigations
• clinical diagnosis, U/S not sensitive for diagnosing abruption (sensitivity = 15%)

Management
• maternal stabilization: large bore IV with hydration, O2 for hypotensive patients
• maternal monitoring: vitals, urine output, blood loss, blood work (hematocrit, CBC, PTT/PT, platelets, fibrinogen, FDP, type and cross match)
• EFM
• blood products on hand (red cells, platelets, cryoprecipitate) because of DIC risk
• Rhogam® if Rh negative
  ▪ Kleihauer-Betke test may confirm abruption
• mild abruption:
  ▪ GA <37 wk: use serial Hct to assess concealed bleeding, deliver when fetus is mature or when hemorrhage dictates
  ▪ GA ≥37 wk: stabilize and deliver
• moderate to severe abruption:
  ▪ hydrate and restore blood loss and correct coagulation defect if present
  ▪ vaginal delivery if no contraindication and no evidence of fetal or maternal distress OR fetal demise
  ▪ C/S if live fetus and fetal or maternal distress develops with fluid/blood replacement, labour fails to progress or if vaginal delivery otherwise contraindicated
Vasa Previa

Definition
- unprotected fetal vessels pass over the cervical os; associated with velamentous insertion of cord into membranes of placenta or succenturiate (accessory) lobe

Epidemiology
- 1 in 5,000 deliveries – higher in twin pregnancies

Clinical Features
- PAINLESS vaginal bleeding and fetal distress (tachy- to bradyarrhythmia)
- 50% perinatal mortality, increasing to 75% if membranes rupture (most infants die of exsanguination)

Investigations
- Apt test (NaOH mixed with the blood) can be done immediately to determine if the source of bleeding is fetal (supernatant turns pink) or maternal (supernatant turns yellow)
- Wright stain on blood smear and look for nucleated red blood cells (in cord, not maternal blood)

Management
- emergency C/S (since bleeding is from fetus, a small amount of blood loss can have catastrophic consequences)

Obstetrical Complications

Preterm Labour

Definition
- uterine contractions intense and frequent enough to cause cervical effacement and dilation between 20 and 37 wk gestation

Etiology
- idiopathic (most common)
- maternal: infection (recurrent pyelonephritis, untreated bacteriuria, chorioamnionitis), HTN, DM, chronic illness, mechanical factors, previous obstetric, gynecological, and abdominal surgeries, socio-environmental (poor nutrition, smoking, drugs, alcohol, stress)
- maternal-fetal: PPROM (common), polyhydramnios, placenta previa, placental abruption, or placental insufficiency
- fetal: multiple gestation, congenital abnormalities of fetus, fetal hydrops, stress
- uterine: incompetent cervix, excessive enlargement (hydramnios, multiple gestation), malformations (leiomyomas, septate uterus, mullerian duct abnormalities, fibroids)

Epidemiology
- preterm labour complicates about 12% of pregnancies, most common cause of neonatal mortality in US

Risk Factors and Prediction of PTL
- maternal risk scoring using above etiologies fails to identify up to 70% of preterm deliveries and is therefore of limited use
- prior history of spontaneous PTL: most important risk factor
- prior history cervical excisions (LEEPs/cone biopsy) or mechanical dilatation (D&C)
- cervical length: measured by transvaginal U/S (cervical length >30 mm has high negative predictive value for PTL before 34 wk)
- identification of bacterial vaginosis (Rx metronidazole if symptomatic or high-risk for PTL) and ureaplasma urealyticum (Rx erythromycin) infections: routine screening not supported by current data but it is reasonable to screen high risk women
- family history of preterm birth
- fetal fibronectin: a glycoprotein in amniotic fluid and placental tissue functioning to maintain integrity of chorionic-decidual interface in asymptomatic women
  - positive if >50 ng/mL
  - in symptomatic women (i.e. preterm contractions), fetal fibronectin is most effectively combined with U/S detecting cervical length
  - if cervical length is not short and fetal fibronectin is negative, preterm labour is highly unlikely
Clinical Features

- regular contractions (2 in 10 min, >6/h)
- cervix >1 cm dilated, >80% effaced, or length <2.5 cm

Management

A. Initial

- transfer to appropriate facility if stable
- hydration (NS at 150 mL/h)
- bed rest in LLDP
- sedation (morphine)
- avoid repeated pelvic exams (increased infection risk)
- U/S examination of fetus (GA, BPP, position, placenta location, estimated fetal weight)
- prophylactic antibiotics; (for GBS) important to consider if PPROM (e.g. erythromycin controversial but may help to delay delivery),

B. Suppression of Labour – Tocolysis

- does not inhibit preterm labour completely, but may delay delivery (used for <48 h) to allow for betamethasone valerate (Celestone®) and/or transfer to appropriate centre for care of the premature infant
- requirements (all must be satisfied)
  - preterm labour
  - live, immature fetus, intact membranes, cervical dilatation of <4 cm
  - absence of maternal or fetal contraindications
- contraindications
  - maternal: bleeding (placenta previa or abruption), maternal disease (HTN, DM, heart disease), preeclampsia or eclampsia, chorioamnionitis
  - fetal: erythroblastosis fetalis, severe congenital anomalies, fetal distress/demise, IUGR, multiple gestation (relative)
- agents
  - calcium channel blockers: nifedipine
    - 20 mg PO loading dose followed by 20 mg PO 90 min later
    - 20 mg can be continued q3-8h for 72 h or to a max of 180 mg
    - 10 mg PO q20min x 4 doses
  - contraindications: nifedipine allergy, hypotension, hepatic dysfunction, concurrent beta-mimetics or MgSO4 use, transdermal nitrites, or other antihypertensive medications
  - prostaglandin synthesis inhibitors: indomethacin
    - 1st line for early preterm labour (<30 wk GA) or polyhydramnios
    - 50-100 mg MR loading dose followed by 50 mg q6h x 8 doses
  - magnesium sulphate was previously used for tocolysis; currently, its primary use in obstetrics is limited to neuroprotection or prevention of eclampsia
    - indicated if preterm delivery is inevitable between 24 and 31+6 wks GA for neuroprotection
    - 4 g IV loading dose followed by 1g q1h maintenance until birth

C. Enhancement of Fetal Pulmonary Maturity

- betamethasone valerate (Celestone®) 12 mg IM q24h x 2 doses or dexamethasone 6 mg IM q12h x 4 doses
  - 28–34 wk GA: reduces incidence of RDS
  - 24–28 wk GA: reduces severity of RDS, overall mortality and rate of IVH
  - specific maternal contraindications: active TB

D. Cervical Cerclage

- definition: placement of cervical sutures at the level of the internal os, usually at the end of the first trimester or in the second trimester and removed in the third trimester
- indications: cervical incompetence (i.e. cervical dilation and effacement in the absence of increased uterine contractility)
  - emerging evidence indicates that progesterone suppositories are superior to cerclage in preventing preterm labour not due to cervical incompetence; (neither is effective in multiple gestations)
- diagnosis of cervical incompetence
  - obstetrical Hx: silent cervical dilatation, 2nd trimester losses, procedures on cervix
  - ability of cervix to hold an inflated Foley catheter during a hysterosonogram
- proven benefit in the prevention of PTL in women with primary structural abnormality of the cervix (e.g. conization of the cervix, connective tissue disorders)

Prognosis

- prematurity is the leading cause of perinatal morbidity and mortality
  - 30 wk or 1,500 g (3.3 lb) = 90% survival
  - 33 wk or 2,000 g (4.4 lb) = 99% survival
- morbidity due to asphyxia, hypoxia, sepsis, RDS, intraventricular cerebral hemorrhage, thermal instability, retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis

Conclusions

- although there are limitations to the studies, there is currently insufficient evidence to support tocolytic therapy for women with PPROM, as there was an increase in maternal chorioamnionitis without significant benefits to the infant.
Prevention of Preterm Labour
• currently there are no agents approved by Health Canada to arrest preterm labour
• preventative measures: good prenatal care, identify pregnancies at risk, treat silent vaginal infection or UTI, patient education
• transvaginal ultrasound of cervical length is recommended only for high-risk pregnancies and only before 30 weeks GA

Premature Rupture of Membranes

Definitions
• PROM: rupture of membranes prior to labour at any GA
• prolonged ROM: >24 h elapsed between rupture of membranes and onset of labour
• preterm ROM: ROM occurring before 37 wk gestation
• PPROM: rupture of membranes before 37 wk AND prior to onset of labour

Risk Factors
• maternal: multiparity, cervical incompetence, infection (cervicitis, vaginitis, STI, UTI), family history of PROM, low socioeconomic class/poor nutrition
• fetal: congenital anomaly, multiple gestation
• other risk factors associated with PTL

Clinical Features
• history of fluid gush or continued leakage

Investigations
• sterile speculum exam (avoid introduction of infection)
  ▪ pooling of fluid in the posterior fornix
  ▪ may observe fluid leaking out of cervix on cough/Valsalva (“cascade”)
• nitrazine (amniotic fluid turns nitrazine paper blue)
  ▪ low specificity as can be positive with blood, urine, or semen
• ferning (high salt in amniotic fluid evaporates, looks like ferns under microscope)
  ▪ U/S to rule out fetal anomalies, assess GA, and BPP
• cultures (lower vagina for GBS)
• L/S ratio (Lecithin:Sphingomyelin Ratio)
  ▪ consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <32 wk and no evidence of infection
  ▪ consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
  ▪ studies show broad spectrum coverage increases the time to onset of labour from PROM by 5-7 d with no increase in maternal or neonatal morbidity or mortality
• deliver urgently if evidence of fetal distress and/or chorioamnionitis

Management
• admit for expectant management and monitor vitals q4h, daily BPP and WBC count
• avoid introducing infection with examinations (do NOT do a bimanual exam)
• cultures (lower vagina for GBS)
• assess fetal lung maturity by L/S ratio of amniotic fluid
  ▪ consider administration of betamethasone valerate (Celestone®) to accelerate maturity if <32 wk and no evidence of infection
  ▪ consider tocolysis for 48 h to permit administration of steroids if PPROM induces labour
  ▪ studies show broad spectrum coverage increases the time to onset of labour from PROM by 5-7 d with no increase in maternal or neonatal morbidity or mortality
• deliver urgently if evidence of fetal distress and/or chorioamnionitis

Table 11. PROM Management

<table>
<thead>
<tr>
<th>Degree of Prematurity</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;24 wk</td>
<td>Consider termination (poor outcome due to pulmonary hypoplasia)</td>
</tr>
<tr>
<td>24-25 wk</td>
<td>Individual consideration with counselling of parents regarding risks to preterm infants</td>
</tr>
<tr>
<td>26-34 wk</td>
<td>Expectant management as prematurity complications are significant</td>
</tr>
<tr>
<td>34-38 wk</td>
<td>“Grey zone” where risk of death from RDS and neonatal sepsis is the same</td>
</tr>
<tr>
<td>≥37 wk</td>
<td>Induction of labour since the risk of death from sepsis is greater than RDS</td>
</tr>
</tbody>
</table>

Prognosis
• varies with gestational age
• 90% of women with PROM at 28-34 wk GA go into spontaneous labour within 1 wk
• 50% of women with PROM at <26 wk GA go into spontaneous labour within 1 wk
• complications: cord prolapse, intrauterine infection (choorioamnionitis), premature delivery, limb contracture
Prolonged Pregnancy

Definition
• pregnancy >42 wk GA

Epidemiology
• 41 wk GA: up to 27%
• >42 wk GA: 5.5%

Etiology
• most cases idiopathic
• anencephalic fetus with no pituitary gland
• placental sulfatase deficiency (X-linked recessive condition in 1/2,000-1/6,000 infants) – rare

Clinical Features
• postmaturity syndrome (10-20% of post-term pregnancies): fetal weight loss, reduced subcutaneous fat, scaling, dry skin from placental insufficiency, long thin body, open-eyed, alert and worried look, long nails, palms and soles wrinkled)
• with increasing GA, higher rates of: intrauterine infection, asphyxia, meconium aspiration syndrome, placental insufficiency, placental aging and infarction, macrosomia, dystocia, fetal distress, operative deliveries, pneumonia, seizures, and requirement of NICU admission

Management
• GA 40-41 wk: expectant management
  • no evidence to support IOL or C/S unless other risk factors for morbidity are present (see prognosis)
• GA >41 wk: offer IOL if vaginal delivery is not contraindicated
  • IOL shown to decrease C/S, fetal heart rate changes, meconium staining, macrosomia, and death when compared with expectant management
• GA >41 wk and expectant management elected: serial fetal surveillance
  • fetal movement count by the mother
  • BPP q3-4d
  • if AFI is decreased, labour should be induced

Prognosis
• if >42 wk, perinatal mortality 2-3x higher (due to progressive uteroplacental insufficiency)
• morbidity increased with HTN in pregnancy, DM, abruption, IU/GR, and multiple gestation

Intrauterine Fetal Death

Definition
• fetal death in utero after 20 wk GA

Epidemiology
• 1% of pregnancies

Etiology
• 50% idiopathic
• 50% secondary to HTN, DM, erythroblastosis fetalis, congenital anomalies, umbilical cord or placental complications, intrauterine infection, APS

Clinical Features
• decreased perception of fetal movement by mother
• SFH and maternal weight not increasing
• absent fetal heart tones on Doppler(not diagnostic)
• high MSAFP
• on U/S: no fetal heart rate. Depending on timing of death may see skull collapse, brain tissue retraction, empty fetal bladder, non-filled aorta, poor visualization of midline flax

Management
• diagnosis: absent cardiac activity and fetal movement on U/S required for diagnosis
• determine secondary cause
  • maternal: HbA1c, fasting glucose, TSH, Kleihauer-Betke, VDRL, ANA, CBC, anticardiolipins, antibody screens, INR/PTT, serum/urine toxicology screens, cervical and vaginal cultures, TORCH screen
  • fetal: karyotype, cord blood, skin biopsy, genetics evaluation, autopsy, amniotic fluid culture for CMV, parvovirus B19, herpes
  • placenta: pathology, bacterial cultures

DIC: Generalized Coagulation and Fibrinolysis Leading to Depletion of Coagulation Factors

Obstetrical Causes
• Abortion
• Gestational HTN
• Fetal demise
• PPH

DIC-specific Blood Work
• Platelets
• aPTT and PT
• FDP
• Fibrinogen

Treatment
• Treat underlying cause
• Supportive
  • Fluids
  • Blood products
    • FFP, platelets, cryoprecipitate
  • Consider anti-coagulation as VTE prophylaxis
**Intrauterine Growth Restriction**

**Definition**
- infant weight <10th percentile for GA or <2,500 g

**Etiology/Risk Factors**
- 50% unknown
- maternal causes
  - malnutrition, smoking, drug abuse, alcoholism, cyanotic heart disease, type 1 DM, SLE, pulmonary insufficiency, previous IUGR (25% risk, most important risk factor), chronic HTN
- maternal-fetal
  - any disease causing placental insufficiency
  - includes gestational HTN, chronic renal insufficiency, gross placental morphological abnormalities (infarction, hemangiomas, placenta previa, placenta accreta, abnormal cord insertion), prolonged gestation
- fetal causes
  - TORCH infections, multiple gestation, congenital anomalies / chromosomal abnormalities (10%)”

**Clinical Features**
- symmetric/type I (25-30%): occurs early in pregnancy
  - reduced growth of both head and abdomen
  - head:abdomen ratio may be normal (>1 up to 32 wk; =1 at 32-34 wk; <1 after 34 wk GA)
  - usually associated with congenital anomalies or TORCH infections
- asymmetric/type II (70%): occurs late in pregnancy
  - fetal abdomen is disproportionately smaller than fetal head
  - brain is spared, therefore head:abdomen ratio increased
  - usually associated with placental insufficiency
  - more favourable prognosis than type I
- complications
  - prone to meconium aspiration, asphyxia, polycythemia, hypoglycemia, hypocalcemia, hyperphosphatemia hyponatremia, and mental retardation
  - greater risk of perinatal morbidity and mortality

**Investigations**
- SFH measurements at every antepartum visit
- if mother at high risk or SFH lags >2 cm behind GA
  - U/S for biparietal diameter, head and abdominal circumference ratio, femur length, fetal weight, and AFV (decrease associated with IUGR)
  - ± BPP
  - Doppler analysis of umbilical cord blood flow

**Management**
- prevention via risk modification prior to pregnancy is ideal
- modify controllable factors: smoking, alcohol, nutrition, and treat maternal illness
- bed rest in LLDP
- serial BPP (monitor fetal growth) and determine cause of IUGR, if possible
- delivery when extrauterine existence is less dangerous than continued intrauterine existence (abnormal function tests, absent growth, severe oligohydramnios) especially if GA >34 wk
- liberal use of C/S since IUGR fetus withstands labour poorly

---

**Macrosomia**

**Definition**
- infant weight >90th percentile for a particular GA or >4,000 g

**Etiology/Risk Factors**
- maternal obesity, GDM, past history of macrosomic infant, prolonged gestation, multiparity
Clinical Features
- increased risk of perinatal mortality
- CPD and birth injuries (shoulder dystocia, fetal bone fracture) more common
- complications of DM in labour (see Table 15, OB28)

Investigations
- serial SFH
- further investigations if mother at high risk or SFH >2 cm ahead of GA
- U/S predictors
  - polyhydramnios
  - third trimester AC >1.5 cm/wk
  - HC/AC ratio <10th percentile
  - FL/AC ratio <20th percentile

Management
- prophylactic C/S is a reasonable option where EFW >5,000 g in non-diabetic woman and EFW >4,500 g in diabetic woman
- no evidence that prophylactic C/S improves outcomes
- early induction of labour is not recommended for non-diabetic mothers
- risks and benefits of early induction (risk of C/S vs. risk of dystocia) must be weighed in diabetic mothers, as current research is unclear

---

**Polyhydramnios/Oligohydramnios**

**Table 12. Polyhydramnios and Oligohydramnios**

<table>
<thead>
<tr>
<th></th>
<th>Polyhydramnios</th>
<th>Oligohydramnios</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>AFI &gt; 25 cm</td>
<td>AFI &lt; 5 cm</td>
</tr>
<tr>
<td></td>
<td>U/S: single deepest pocket &gt; 8 cm</td>
<td>U/S: single deepest pocket ≤ 2 cm</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Idiopathic most common</td>
<td>Idiopathic most common</td>
</tr>
<tr>
<td></td>
<td>Maternal</td>
<td>Maternal</td>
</tr>
<tr>
<td></td>
<td>• Type 1 DM: abnormalities of transchorionic flow</td>
<td>• Uteroplacental insufficiency (preeclampsia, nephropathy)</td>
</tr>
<tr>
<td></td>
<td>• Chorioangiomas</td>
<td>• Medications (ACEI)</td>
</tr>
<tr>
<td></td>
<td>• Multiple gestation</td>
<td>• Fetal</td>
</tr>
<tr>
<td></td>
<td>• Fetal hydrops (increased erythroblastosis)</td>
<td>• Congenital urinary tract anomalies (renal agenesis, obstruction, posterior</td>
</tr>
<tr>
<td></td>
<td>•  Chromosomal anomaly (up to 2/3 of fetuses have severe polyhydramnios)</td>
<td>urethral valves)</td>
</tr>
<tr>
<td></td>
<td>• Respiratory: cystic adenomatoid malformed lung</td>
<td>• Demise/chronic hypoxemia (blood shunt away from kidneys to perfuse brain)</td>
</tr>
<tr>
<td></td>
<td>• CNS: anencephaly, hydrocephalus, meningocoele</td>
<td>• IUlr</td>
</tr>
<tr>
<td></td>
<td>• GI: tracheoesophageal fistula, duodenal atresia, facial clefts (interfere</td>
<td>• Ruptured membranes; prolonged amniotic fluid leak</td>
</tr>
<tr>
<td></td>
<td>with swallowing)</td>
<td>• Amniotic fluid normally decreases after 35 wk</td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
<td>Occur in 0.2-1.6% of all pregnancies</td>
<td>Occur in ~4.5% of all pregnancies</td>
</tr>
<tr>
<td></td>
<td>Common in pregnancies &gt; 41 wk (~12%)</td>
<td>Severe form in &lt; 0.7%</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>Uterus large for dates, difficulty palpating fetal parts and hearing FHR</td>
<td>Uterus small for dates</td>
</tr>
<tr>
<td>Features and</td>
<td>Maternal complications</td>
<td>Fetal complications</td>
</tr>
<tr>
<td>Complications</td>
<td>• Pressure symptoms from overdistended uterus</td>
<td>• 15-25% have fetal anomalies</td>
</tr>
<tr>
<td></td>
<td>(dyspnea, edema, hydronephrosis)</td>
<td>• Amniotic fluid bands (T1) can lead to Potter’s facies, limb deformities,</td>
</tr>
<tr>
<td></td>
<td>Obstetrical complications</td>
<td>abdominal wall defects</td>
</tr>
<tr>
<td></td>
<td>• Cord prolapse, placental abruption, malpresentation, preterm labour,</td>
<td>Obstetrical complications</td>
</tr>
<tr>
<td></td>
<td>uterine dysfunction, and PPH</td>
<td>• Cord compression</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increased risk of adverse fetal outcomes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pulmonary hypoplasia (late-onset)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Marker for infants who may not tolerate labour well</td>
</tr>
<tr>
<td><strong>Management</strong></td>
<td>Determine underlying cause:</td>
<td>Always warrants admission and investigation:</td>
</tr>
<tr>
<td></td>
<td>• Screen for maternal disease/infection</td>
<td>• Rule out ROM</td>
</tr>
<tr>
<td></td>
<td>• Complete fetal U/S evaluation</td>
<td>• Fetal monitoring (NST, BPP)</td>
</tr>
<tr>
<td></td>
<td>Depends on severity</td>
<td>• U/S Doppler studies (umbilical cord and uterine artery)</td>
</tr>
<tr>
<td></td>
<td>• Mild to moderate cases require no treatment</td>
<td>Maternal hydration with oral or IV fluids to help increase amniotic fluid</td>
</tr>
<tr>
<td></td>
<td>• If severe, hospitalize and consider therapeutic amniocentesis</td>
<td>Vesicovasomniotic shunt: if etiology is related to fetal obstructive uropathy;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>however, pulmonary function may not be restored with restoration of amniotic fluid</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Injection of fluid via amniocentesis will improve condition for ~1 wk – may be</td>
</tr>
<tr>
<td></td>
<td></td>
<td>most helpful for visualizing any associated fetal anomalies</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Consider delivery if term</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amnio-infusion may be considered during labour via intrauterine catheter</td>
</tr>
<tr>
<td><strong>Prognosis</strong></td>
<td>2-5 fold increase in risk of perinatal mortality</td>
<td>Poorer with early onset</td>
</tr>
<tr>
<td></td>
<td>High mortality related to congenital malformations and pulmonary hypoplasia</td>
<td>when diagnosed during T2</td>
</tr>
</tbody>
</table>

Pregnancy Complications
Multi-Fetal Gestation and Malpresentation

**Epidemiology**
- incidence of twins is 1/80 and triplets 1/6,400 in North America
- 2/3 of twins are dizygotic (fraternal)
  - risk factors for dizygotic twins: IVF, increased maternal age, newly discontinued OCP, ethnicity (e.g. certain African regions)
- monozygous twinning occurs at a constant rate worldwide (1/250)
- determine zygosity by number of placentas, thickness of membranes, sex, blood type

**Clinical Features**

**Table 13. Complications Associated with Multiple Gestation**

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Uteroplacental</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperemesis gravidum</td>
<td>Increased PROM/PTL</td>
<td>Prematurity*</td>
</tr>
<tr>
<td>GDM</td>
<td>Polyhydramnios</td>
<td>IUGR</td>
</tr>
<tr>
<td>Gestational HTN</td>
<td>Placenta previa</td>
<td>Malpresentation</td>
</tr>
<tr>
<td>Anemia</td>
<td>Placental abruption</td>
<td>Congenital anomalies</td>
</tr>
<tr>
<td>Increased physiological stress on all systems</td>
<td>PPH (uterine atony)</td>
<td>Twin-twin transfusion</td>
</tr>
<tr>
<td>Increased compressive symptoms</td>
<td>Umbilical cord prolapse</td>
<td>Increased perinatal morbidity and mortality</td>
</tr>
<tr>
<td>C/S</td>
<td>Cord anomalies (velamentous insertion, 2 vessel cord)</td>
<td>Twin interlocking (twin A breech, twin B vertex)</td>
</tr>
</tbody>
</table>

*Most common cause of perinatal mortality in multiple gestation

**Management**
- U/S determination of chorionicity must be done within first trimester (ideally 8-12 wk GA)
- increased antenatal surveillance
  - serial U/S q 2-3wk from 24 wk GA to assess growth (uncomplicated diamniotic dichorionic)
  - increased frequency of ultrasounds in monochorionic diamniotic and monochorionic monoamniotic twins
  - Doppler flow studies weekly if discordant fetal growth (>30%)
  - BPP as needed
- may attempt vaginal delivery if twin A presents as vertex, otherwise C/S (40-50% of all twin deliveries, 15% of cases have twin A delivered vaginally and twin B delivered by C/S)
- mode of delivery depends on fetal weight, GA, presentation

**Figure 4. Classification of twin pregnancies**

*Indicates time of cleavage
**Twin-Twin Transfusion Syndrome**

**Epidemiology**
- 10% of monochorionic twins
- concern if >30% discordance in estimated fetal weight

**Etiology**
- arterial blood from donor twin passes through placenta into vein of recipient twin

**Clinical Features**
- donor twin: IUGR, hypovolemia, hypotension, anemia, oligohydramnios
- recipient twin: hypervolemia, HTN, CHF, polycythemia, edema, polyhydramnios, kernicterus in neonatal period

**Investigations**
- detected by U/S screening, Doppler flow analysis

**Management**
- therapeutic serial amniocentesis to decompress polyhydramnios of recipient twin and decrease pressure in cavity and on placenta
- intrauterine blood transfusion to donor twin if necessary
- laparoscopic occlusion of placental vessels

---

**Breech Presentation**

**Definition**
- fetal buttocks or lower extremity is the presenting part as determined on U/S
- complete (10%): hips and knees both flexed
- frank (60%): hips flexed, knees extended, buttocks present at cervix
  - most common type of breech presentation
  - most common breech presentation to be delivered vaginally
- incomplete (30%): both or one hip flexed and both or one knee present below the buttocks, feet or knees present first (footling breech, kneeling breech)

**Epidemiology**
- occurs in 3-4% of pregnancies at term (25% <28 wk)

**Risk Factors**
- maternal: pelvis (contracted), uterus (shape abnormalities, intrauterine tumours, fibroids, previous breech), pelvic tumours causing compression, grand multiparity
- maternal-fetal: placenta (previa), amniotic fluid (poly-/oligohydramnios)
- fetal: prematurity, multiple gestation, congenital malformations (found in 6% of breeches; 2-3% if in vertex presentations), abnormalities in fetal tone and movement, aneuploidy, hydrocephalus, anencephalus

**Management**
- ECV: repositioning of singleton fetus within uterus under U/S guidance
  - overall success rate of 65%
  - criteria: >36 wk GA, singleton, unengaged presenting part, reactive NST, not in labour
  - contraindications: previous T3 bleed, prior classical C/S, previous myomectomy, oligohydramnios, PROM, placenta previa, abnormal U/S, suspected IUGR, HTN, uteroplacental insufficiency, nuchal cord
  - risks: abruption, cord compression, cord accident, ROM, labour, fetal bradycardia requiring C/S (<1% risk), alloimmunization, fetal death 1:5,000
  - method: tocometry, followed by U/S guided transabdominal manipulation of fetus with constant fetal heart monitoring
  - if patient Rh negative, give Rhogam® prior to procedure
  - good prognostic factors (for a successful version)
    - multiparous, good fluid volume, small baby, skilled obstetrician, posterior placenta
    - pre- or early labour ultrasound to assess type of breech presentation, fetal growth, estimated weight, placenta position, attitude of fetal head (flexed is preferable); if ultrasound unavailable, recommend C/S
- ECV and elective C/S should be presented as options with the risks and benefits outlined; obtain informed consent
- method for vaginal breech delivery
  - encourage effective maternal pushing efforts
  - at delivery of after-coming head, assistant must apply suprapubic pressure to flex and engage fetal head
  - delivery can be spontaneous or assisted; avoid fetal traction
  - apply fetal manipulation only after spontaneous delivery to level of umbilicus

---

**Figure 5. Types of breech presentation**

**Criteria for Vaginal Breech Delivery**
- Frank or complete breech, GA >36 wk
- EFW 2,500-3,800 g based on clinical and U/S assessment (5.5–8.5 lb)
- Fetal head flexed
- Continuous fetal monitoring
- 2 experienced obstetricians, assistant, and anesthetist present
- Ability to perform emergency C/S within 30 min if required
Vaginal Delivery of Breech Presentation
SOGC Clinical Practice Guidelines 2009;226:557-566
Objective: To discuss risks and benefits of trial of labour versus planned C/S, with selection criteria, management, and delivery techniques for trial of vaginal breech birth.
Evidence: Randomized trials, prospective cohort studies and select cohort studies from Medline search for long-term outcomes and epidemiology of vaginal breech delivery.
Summary: Higher risk of perinatal mortality and short-term neonatal morbidity can be associated with vaginal breech birth as compared to elective C/S. However, careful case selection (including term singleton breech fetuses and clinically adequate maternal pelvis) and labour management may achieve a similar safety level as elective C/S (~2 per 1,000 births perinatal mortality, ~2% short-term neonatal morbidity). Specific protocols for vaginal breech delivery should be followed: continuous fetal heart monitoring, assessment for adequate progress in labour, no induction of labour recommended, emergency C/S available, if required, and health care providers with requisite skills and experience. Informed consent for the preferred delivery method should be obtained.

Hypertensive Disorders of Pregnancy

Hypertension in Pregnancy

• hypertensive disorders of pregnancy are classified as either pre-existing or gestational HTN

PRE-EXISTING HYPERTENSION

Definition
• BP >140/90 prior to 20 wk GA, persisting >7 wk postpartum
• essential HTN is associated with an increased risk of gestational HTN, abruptio placentae, IUGR, and IUFD

GESTATIONAL HTN

Definition
• sBP >140 or dBP >90 developing after 20th wk GA in a woman known to be normotensive before pregnancy

Risk Factors
• maternal factors
  ▪ primigravida (80-90% of gestational HTN)
  ▪ first conception with a new partner
  ▪ PMHx or FHx of gestational HTN
  ▪ DM, chronic HTN, or renal insufficiency
  ▪ antiphospholipid syndrome
  ▪ extremes of maternal age (<18 or >35 yr)
  ▪ previous stillbirth or IUFD
• fetal factors
  ▪ IUGR or oligohydramnios
  ▪ GTN
  ▪ multiple gestation
  ▪ fetal hydrops

Clinical Evaluation of HTN in Pregnancy
• in general, clinical evaluation should include the mother and fetus
  • evaluation of mother
    ▪ body weight
    ▪ central nervous system
      ▪ presence and severity of headache
      ▪ visual disturbances – blurring, scotomata
      ▪ tremulousness, irritability, somnolence
      ▪ hyperreflexia
    ▪ hematologic
      ▪ bleeding, petechiae
    ▪ hepatic
      ▪ RUQ or epigastric pain
      ▪ severe N/V
    ▪ renal
      ▪ urine output and colour
      ▪ non-dependent edema (i.e. hands and face)
  • evaluation of fetus
    ▪ fetal movement
    ▪ fetal heart rate tracing – NST
    ▪ ultrasound for growth
    ▪ BPP
    ▪ Doppler flow studies

Adverse Maternal Conditions
• sBP >160 mmHg
• dBP >100 mmHg
• HELLP
• Cerebral hemorrhage
• Renal dysfunction: oliguria <500 mL/d
• Left ventricular failure, pulmonary edema
• Placental abruption, DIC

Symptoms
• Abdominal pain, N/V
• Headaches, visual problems
• SOB, chest pain
• Eclampsia: convulsions

Adverse Fetal Conditions
• IUGR
• Oligohydramnios
• Absent/reversed umbilical artery end diastolic flow

Can result in:
• Fetal disability and/or death

Ominous Symptoms of HTN in Pregnancy
RUQ pain, headache, and visual disturbances

Hypertension in Pregnancy

Adverse Maternal Conditions
• sBP >160 mmHg
• dBP >100 mmHg
• HELLP
• Cerebral hemorrhage
• Renal dysfunction: oliguria <500 mL/d
• Left ventricular failure, pulmonary edema
• Placental abruption, DIC

Symptoms
• Abdominal pain, N/V
• Headaches, visual problems
• SOB, chest pain
• Eclampsia: convulsions

Adverse Fetal Conditions
• IUGR
• Oligohydramnios
• Absent/reversed umbilical artery end diastolic flow

Can result in:
• Fetal disability and/or death
Laboratory Evaluation of Gestational Hypertension
- CBC
- PTT, INR, fibrinogen – especially if surgery or regional anesthetics are planned
- ALT, AST
- creatinine, uric acid
- 24 h urine collection for protein or albumin:creatinine ratio

Complications
- maternal
  - liver and renal dysfunction
  - seizure
  - abruptio placenta
  - left ventricular failure/pulmonary edema
  - DIC (release of placental thromboplastin consumptive coagulopathy)
  - HELLP syndrome
- treat with FFP infusion or plasma exchange
- hemorrhagic stroke (50% of deaths)
- fetal
  - IUGR, prematurity, abruptio placenta, IUFD

Management
- for non-severe HTN (149-159/90-105) target a BP of 130-155/80-105 in women without comorbidities or <140/90 in women with comorbidities
- for both pre-existing and gestational HTN, labetalol 100-400 mg PO bid-tid, nifedipine XL preparation 20-60 mg PO od, or α-methyldopa 250-300 mg PO bid-qid
- for severe HTN (BP>160/110), give one of:
  - labetalol 20 mg IV then 20-80 mg IV q30min (max 300 mg)(then switch to oral)
  - nifedipine 5-10 mg capsule q30min
  - hydralazine 5 mg IV, repeat 5-10 mg IV q30min or 0.5 to 10 mg/hr IV, to a maximum of 20 mg IV (or 30 mg IM)
- no ACEI, ARBs, diuretics, prazosin, or atenolol
- pre-existing HTN and gestational HTN without any deterioration can be followed until 37 wk then decide to induce shortly thereafter

PREECLAMPSIA

Definition
- pre-existing or gestational HTN with new onset proteinuria or adverse conditions

Risk Factors
- nulliparity
- preeclampsia in a previous pregnancy
- age >40 yr or <18 yr
- FHx of preeclampsia
- chronic HTN
- chronic renal disease
- antiphospholipid antibody syndrome or inherited thrombophilia
- vascular or connective tissue disease
- DM (pre-gestational and gestational)
- high BMI
- hydrops fetalis
- unexplained fetal growth restriction
- abruptio placenta
- there is a potential for further deterioration to severe preeclampsia as defined above
- the adverse conditions are many and include both maternal and fetal issues

Management
- depends on GA, possible threat of seizures (check reflexes)
- if stable and no adverse factors, may admit and follow, ± decide to deliver as approaching 34-36 wk (must weigh risks of fetal prematurity vs. risks of developing severe preeclampsia/eclampsia)
- for severe preeclampsia, stabilize and deliver
- if severe preeclampsia during labour, increase maternal monitoring: hourly input and output, urine dip q12h, hourly neurological vitals, and increase fetal monitoring (continuous FHR monitoring)
- antihypertensive therapy
  - labetalol 20 mg IV then 20-80 mg IV q30min (max 300 mg)(then switch to oral)
  - nifedipine 5-10 mg capsule q30min
  - hydralazine 5 mg IV, repeat 5-10 mg IV q30min or 0.5 to 10 mg/hr IV, to a maximum of 20 mg IV (or 30 mg IM)
• seizure prevention
  • MgSO₄
  • postpartum management
  • risk of seizure highest in first 24 h postpartum – continue MgSO₄ for 12-24 h after delivery
  • vitals q1h
  • consider HELLP syndrome in toxic patients
  • most return to a normotensive BP within 2 wk

ECLAMPSIA

Definition
• the occurrence of one or more generalized convulsions and/or coma in the setting of preeclampsia and in the absence of other neurologic conditions

Epidemiology
• an eclamptic seizure occurs in approximately 0.5% of mildly preeclamptic women and 2-3% of severely preeclamptic women

Risk Factors
• same as risk factors for preeclampsia

Clinical Manifestations
• eclampsia is a clinical diagnosis
• typically tonic-clonic and lasting 60-75 s
• one of the signs of an impending seizure is hyperreflexia
• symptoms that may occur before the seizure include persistent frontal or occipital headache, blurred vision, photophobia, right upper quadrant or epigastric pain, and altered mental status
• in up to one third of cases, there is no proteinuria or blood pressure <140/90 mmHg prior to the seizure
• in general, women with typical eclamptic seizures who do not have focal neurologic deficits or prolonged coma do not require diagnostic evaluation including imaging

Management
• ABCs
• roll patient into LLDP
• supplemental O₂ via face mask to treat hypoxemia due to hypoventilation during convulsive episode
• aggressive antihypertensive therapy for sustained diastolic pressures ≥105 mmHg or systolic blood pressures ≥160 mmHg with hydralazine or labetalol
• prevention of recurrent convulsions: to prevent further seizures and the possible complications of repeated seizure activity (e.g. rhabdomyolysis, metabolic acidosis, aspiration pneumonitis, etc.)
• MgSO₄ is now the drug of choice, with previously used agents including diazepam and phenytoin
• the definitive treatment of eclampsia is DELIVERY, irrespective of gestational age, to reduce the risk of maternal morbidity and mortality from complications of the disease
• mode of delivery is dependent on clinical situation and fetal-maternal condition

Iron and Folate Deficiency Anemia

<table>
<thead>
<tr>
<th>Table 14. Iron Deficiency and Folate Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Iron Deficiency Anemia</strong></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
</tr>
</tbody>
</table>
Table 14. Iron Deficiency and Folate Deficiency Anemia (continued)

<table>
<thead>
<tr>
<th>Iron Deficiency Anemia</th>
<th>Folate Deficiency Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Management</td>
<td>Prevention: 0.4-1 mg folic acid PO daily for 1-3 mo preconceptually and throughout T1, or 5 mg folic acid per day with past history of oNTD, DM, or antiepileptic medication use</td>
</tr>
<tr>
<td></td>
<td>Prevention (non-anemic): 30 mg elemental iron/d (met by most prenatal vitamins)</td>
</tr>
<tr>
<td></td>
<td>Treatment (anemic): 30-120 mg elemental iron/d</td>
</tr>
<tr>
<td></td>
<td>325 mg ferrous fumarate = 106 mg elemental Fe2⁺; 325 mg ferrous sulfate = 65 mg elemental Fe2⁺; 325 mg ferrous gluconate = 36 mg elemental Fe2⁺</td>
</tr>
<tr>
<td></td>
<td>Polysaccharide-Iron Complex = 150 mg elemental Fe/capsule</td>
</tr>
<tr>
<td>Complications</td>
<td>Maternal: decreased blood volume, N/V, anorexia</td>
</tr>
<tr>
<td></td>
<td>Fetal: neural tube defects in T1, low birth weight</td>
</tr>
<tr>
<td></td>
<td>Maternal: angina, CHF, infection, slower recuperation, preterm labour</td>
</tr>
<tr>
<td></td>
<td>Fetal: decreased oxygen carrying capacity leading to fetal distress, IUGR, and low birth weight</td>
</tr>
<tr>
<td>Notes</td>
<td>Mother needs 1 g of elemental iron per fetus; this amount exceeds normal stores + dietary intake</td>
</tr>
<tr>
<td></td>
<td>Iron requirements increase during pregnancy due to fetal/placental growth (500 mg), increased maternal RBC mass (500 mg), and losses (200 mg) – more needed for multiple gestations</td>
</tr>
<tr>
<td></td>
<td>Minimum daily requirement is 0.4 mg</td>
</tr>
<tr>
<td></td>
<td>Most often associated with iron deficiency anemia</td>
</tr>
<tr>
<td></td>
<td>Folic acid is necessary for closure of neural tube during early fetal development (by day 28 of gestation)</td>
</tr>
</tbody>
</table>

Diabetes Mellitus

Epidemiology
- 2-4% of pregnancies are complicated by DM

Classification of Diabetes Mellitus
- type 1 and type 2 DM (see Endocrinology, E7)
- GDM: onset of DM during pregnancy (usually around 24-28 wk GA)

Etiology
- type 1 and type 2 DM
- GDM: anti-insulin factors produced by placenta and high maternal cortisol levels create increased peripheral insulin resistance → leading to GDM and/or exacerbating pre-existing DM

MANAGEMENT

A. TYPE 1 and TYPE 2 DM

Preconception
- pre-plan and refer to high-risk clinic
- optimize glycemic control
- counsel patient on potential risks and complications
- evaluate for diabetic retinopathy, neuropathy, CAD

Pregnancy
- if already on oral medication, generally switch to insulin therapy
  - continuing glyburide or metformin controversial
  - teratogenicity unknown for other oral anti-hyperglycemics
- tight glycemic control
  - insulin dosage may need to be adjusted in T2 due to increased demand and increased insulin resistance
- monitor as for normal pregnancy plus initial 24 h urine protein and creatinine clearance, retinal exam, HbA1c
  - HbA1c: >140% of pre-pregnancy value associated with increased risk of spontaneous abortion and congenital malformations
  - increased fetal surveillance (BPP, NST), consider fetal ECHO to look for cardiac abnormalities

Labour
- timing of delivery depends on fetal and maternal health and risk factors (i.e. must consider size of baby, lung maturity, maternal blood glucose, and blood pressure control)
- can wait for spontaneous labour if blood glucose well-controlled and BPP normal
- induce by 38 wk
• type of delivery
  ▪ increased risk of cephalopelvic disproportion (CPD) and shoulder dystocia with babies >4,000 g (8.8 lbs)
  ▪ elective C/S for predicted birthweight >4,500 g (9.9 lbs) (controversial)
• monitoring
  ▪ during labour monitor blood glucose q1h with patient on insulin and dextrose drip
  ▪ aim for blood glucose between 3.5-6.5 mmol/L to reduce the risk of neonatal hypoglycemia

Postpartum
• insulin requirements dramatically drop with expulsion of placenta (source of insulin antagonists)
• no insulin is required for 48-72 h postpartum in most type 1 DM
• monitor glucose q6h, restart insulin at two-thirds of pre-pregnancy dosage when glucose >8 mmol/L

B. GESTATIONAL DM

Screening and Diagnosis
• all pregnant women between 24-28 wk GA (or at any stage if high risk)
• 2 screening options
  ▪ 1-step screening with fasting 75 g OGTT; GDM if ≥1 of:
    ▪ FPG ≥ 5.1 mmol/L
    ▪ 1h PG ≥ 10.0 mmol/L
    ▪ 2h PG ≥ 8.5 mmol/L
  ▪ 2-step screening
    ▪ Step 1: Perform a random nonfasting 50 g OGCT
      – 1h PG < 7.8 mmol/L is normal
      – 1h PG ≥ 11.1 mmol/L is GDM
      – if 1h PG 7.8-11.0 mmol/L, proceed to Step 2
    ▪ Step 2: Perform a fasting 75 g OGTT, GDM if ≥1 of:
      – FPG ≥ 5.3 mmol/L
      – 1h PG ≥ 10.6 mmol/L
      – 2h PG ≥ 9.0 mmol/L

Management
• first line is management through diet modification and increased physical activity
• initiate insulin therapy if glycemic targets not achieved within 2 wk of lifestyle modification alone
• glycemic targets: FPG <5.3 mmol/L, 1h PG <7.8 mmol/L, 2h PG <6.7 mmol/L
• use of oral agents can be used in pregnancy but is off-label and should be discussed with patient
• stop insulin and diabetic diet postpartum
• 6 wk postpartum visit: follow up with 75 g OGTT, counsel about lifestyle modifications, and perform glucose challenge test q2 yr

Prognosis
• most maternal and fetal complications are related to hyperglycemia and its effects

Long-Term Maternal Complications
• type 1 and type 2 DM: risk of progressive retinopathy and nephropathy
• GDM: 50% risk of developing type 2 DM in next 20 yr

Table 15. Complications of DM in Pregnancy

<table>
<thead>
<tr>
<th>Maternal</th>
<th>Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstetric</td>
<td>Growth Abnormalities</td>
</tr>
<tr>
<td>HTN/preeclampsia (especially if pre-existing nephropathy/proteinuria): insulin resistance is implicated in etiology of HTN</td>
<td>Macrosomia: maternal hyperglycemia leads to fetal hyperinsulinism resulting in accelerated anabolism</td>
</tr>
<tr>
<td>Polyhydramnios: maternal hyperglycemia leads to fetal hyperglycemia, which leads to fetal polyuria (a major source of amniotic fluid)</td>
<td>IUGR: due to placental vascular insufficiency</td>
</tr>
<tr>
<td>Diabetic Emergencies</td>
<td>Delayed Organ Maturity</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Fetal lung immaturity: hyperglycemia interferes with surfactant synthesis (respiratory distress syndrome)</td>
</tr>
<tr>
<td>Ketoadosis</td>
<td>Diabetic coma</td>
</tr>
<tr>
<td>Diabetic coma</td>
<td>End-Organ Involvement or Deterioration (occur in type 1 DM and type 2 DM, not in GDM)</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Congenital Anomalies (occur in type 1 DM and type 2 DM, not in GDM)</td>
</tr>
<tr>
<td>Nephropathy</td>
<td>• 2-7x increased risk of cardiac (VSD), NTD, GU (cystic kidneys), GI (anal atresia), and MSK (sacral agenesis) anomalies due to hyperglycemia</td>
</tr>
<tr>
<td></td>
<td>• Note: Pregnancies complicated by GDM do not manifest an increased risk of congenital anomalies because GDM develops after the critical period of organogenesis (in T1)</td>
</tr>
</tbody>
</table>
Table 15. Complications of DM in Pregnancy (continued)

<table>
<thead>
<tr>
<th>Maternal Fetal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Labour and Delivery</td>
</tr>
<tr>
<td>• Preterm labour/prematurity: most commonly in patients with HTN/preeclampsia</td>
</tr>
<tr>
<td>• Preterm labour is associated with poor glycemic control but the exact mechanism is unknown</td>
</tr>
<tr>
<td>• Increased incidence of stillbirth</td>
</tr>
<tr>
<td>• Birth trauma: due to macrosomia, can lead to difficult vaginal delivery and shoulder dystocia</td>
</tr>
<tr>
<td>Neonatal</td>
</tr>
<tr>
<td>• Hypoglycemia: due to pancreatic hyperplasia and excess insulin secretion in the neonate</td>
</tr>
<tr>
<td>• Hyperbilirubinemia and jaundice: due to prematurity and polycythemia</td>
</tr>
<tr>
<td>• Hypocalcemia: exact pathophysiology not understood, may be related to functional hypoparathyroidism</td>
</tr>
<tr>
<td>• Polycythemia: hyperglycemia stimulates fetal erythropoietin production</td>
</tr>
</tbody>
</table>

**Group B Streptococcus**

**Epidemiology**
- 15–40% vaginal carrier rate

**Risk Factors (for neonatal disease)**
- GBS bacteriuria during current pregnancy even if treated
- previous infant with invasive GBS infection
- preterm labour <37 wk
- ruptured membranes >18 h before delivery
- intrapartum maternal temperature ≥38°C
- positive GBS screen during current pregnancy

**Clinical Features**
- not harmful to mother
- risk of vertical transmission (neonatal sepsis, meningitis or pneumonia, and death)

**Investigations**
- offer screening to all women at 35–37 wk with vaginal and anorectal swabs for GBS culture

**Treatment**
- treatment of maternal GBS at delivery decreases neonatal morbidity and mortality
- indications for antibiotic prophylaxis: positive GBS screen, GBS in urine, or previous infant with GBS disease or GBS status unknown and one of the other risk factors
- antibiotics for GBS prophylaxis
  - penicillin G 5 million units IV then 2.5 million units IV q4h until delivery
  - penicillin allergic but not at risk for anaphylaxis: cefazolin 2 g IV then 1 g q8h
  - penicillin allergic and at risk for anaphylaxis: vancomycin 1 g IV q12h until delivery
- if fever, broad spectrum antibiotic coverage is advised

**Urinary Tract Infection**

**Epidemiology**
- most common medical complication of pregnancy
- asymptomatic bacteriuria in 2–7% of pregnant women, more frequently in multiparous women
- note: asymptomatic bacteriuria should be treated in pregnancy due to increased risk of pyelonephritis and preterm labour

**Etiology**
- increased urinary stasis from mechanical and hormonal (progesterone) factors
- organisms include GBS as well as those that occur in non-pregnant women

**Clinical Features**
- may be asymptomatic
- dysuria, urgency, and frequency in cystitis
- fever, flank pain, and costovertebral angle tenderness in pyelonephritis

**Investigations**
- urinalysis, urine C&S
- cystoscopy and renal function tests in recurrent infections
### Infections During Pregnancy

<table>
<thead>
<tr>
<th>Table 16. Infections During Pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infection</strong></td>
</tr>
<tr>
<td>--------------</td>
</tr>
<tr>
<td>Chicken Pox</td>
</tr>
<tr>
<td><em>CMV</em></td>
</tr>
<tr>
<td>Erythema Infectiosum (Fifth Disease)</td>
</tr>
<tr>
<td>Hepatitis B</td>
</tr>
<tr>
<td><em>Herpes Simplex Virus</em></td>
</tr>
<tr>
<td>HIV</td>
</tr>
</tbody>
</table>

### Management
- uncomplicated UTI
  - first line: amoxicillin (250-500 mg PO q8h x 7 d)
  - alternatives: nitrofurantoin (100 mg PO bid x 7 d)
  - follow with monthly urine cultures
- pyelonephritis
  - hospitalization and IV antibiotics

### Prognosis
- complications if untreated: acute cystitis, pyelonephritis, and possible preterm labour
- recurrence is common
Table 16. Infections During Pregnancy (continued)

<table>
<thead>
<tr>
<th>Infection</th>
<th>Agent</th>
<th>Source of Transmission</th>
<th>Greatest Transmission Risk to Fetus</th>
<th>Effects on Fetus</th>
<th>Effects on Mother</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Rubella</td>
<td>ssRNA togavirus</td>
<td>To mom: respiratory droplets (highly contagious)</td>
<td>T1</td>
<td>SA or congenital rubella syndrome (hearing loss, cataracts, CV lesions, MR, IUGR, hepatitis, CNS defects, osseous changes)</td>
<td>Rash (50%), fever, posterior auricular or occipital lymphadenopathy, arthralgia</td>
<td>Serologic testing; all pregnant women screened (immune if titre &gt;1:16); infection if IgM present or &gt;4x increase in IgG</td>
<td>No specific treatment; offer vaccine following pregnancy Do not administer during pregnancy (live attenuated)</td>
</tr>
<tr>
<td>Syphilis</td>
<td>Spirochete (<em>Treponema pallidum</em>)</td>
<td>To mom: sexual contact</td>
<td>T1-T3</td>
<td>Risk of preterm labour, multisystem involvement, fetal death</td>
<td>See Infectious Diseases, ID25</td>
<td>VDRL screening for all pregnancies; if positive, requires confirmatory testing</td>
<td>Pen G 2.4 million U IM x 1 dose if early syphilis, 3 doses if late syphilis, monitor VDRL monthly If Pen G allergic: Clindamycin 900 mg IV q8h</td>
</tr>
<tr>
<td><em>Toxoplasmosis</em></td>
<td>Protozoa (<em>Toxoplasma gondii</em>)</td>
<td>To mom: raw meat, unpasteurized goat’s milk, cat feces/urine To baby: transplacental</td>
<td>T3 (but most severe if infected in T1); only concern if primary infection during pregnancy</td>
<td>Congenital toxoplasmosis (chorioretinitis, hydrocephaly, intracranial calcification, MR, microcephaly) NR: 75% initially asymptomatic at birth</td>
<td>Majority subclinical; may have flu-like symptoms</td>
<td>IgM and IgG serology; PCR of amniotic fluid</td>
<td>Self-limiting in mother; spiramycin decreases fetal morbidity but not rate of transmission</td>
</tr>
</tbody>
</table>

* Indicates TORCH infection

Venous Thromboembolism

Epidemiology
- incidence of 12.1/10,000 (DVT), and 5.4/10,000 (PE)
- increased risk VTE throughout pregnancy with highest risk of DVT in third trimester and postpartum period and highest risk of PE post-partum (first 6 weeks)

Risk Factors
- previous VTE, age >35, obesity, infection, bedrest/immobility, shock/dehydration, thrombophilias (see Hematology, H35)

Table 17. Risk Factors for VTE Specific to Pregnancy

<table>
<thead>
<tr>
<th>Hypercoagulability</th>
<th>Stasis</th>
<th>Endothelial</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased factors:</td>
<td>Increased resistance to activated protein C</td>
<td>Vascular damage at delivery (C/S or SV)</td>
</tr>
<tr>
<td>II, V, VII, VIII, IX, X, XII fibrinogen</td>
<td>Antithrombin can be normal or reduced increased venous distensibility</td>
<td>Uterine instrumentation</td>
</tr>
<tr>
<td>Increased platelet aggregation</td>
<td>Decreased venous tone</td>
<td>Peripartum pelvic surgery</td>
</tr>
<tr>
<td>Decreased protein S, tPA, factors XI, XIII</td>
<td>50% decrease in venous flow in lower extremity by T3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Uterus is mechanical impediment to venous return</td>
<td></td>
</tr>
</tbody>
</table>

Clinical Features
- most DVTs occur in the iliofemoral or calf veins with a predilection for the left leg
- signs of a pulmonary embolism are non-specific (as in non-pregnant women)
- unexplained spontaneous fetal loss

Investigations
- duplex venous Doppler sonography for DVT
- CXR and V/Q scan or spiral CT for PE

Management
- before initiating treatment, obtain a baseline CBC including platelets, and aPTT
- warfarin is contraindicated during pregnancy due to its potential teratogenic effects
- unfractionated heparin
  - bolus of 5,000 IU followed by an infusion of ~30,000 IU/24h
  - measure aPTT 6 h after the bolus
Normal Labour and Delivery

Definition of Labour

- true labour: regular, painful contractions of increasing intensity associated with progressive dilatation and effacement of cervix and descent of presenting part, or progression of station
  - preterm (>20 to <36+6 wk GA)
  - term (37-41+6 wk GA)
  - postterm (>42 wk GA)
- false labour: Braxton-Hicks contractions
  - irregular contractions, with unchanged intensity and long intervals, occur throughout pregnancy and not associated with any cervical dilatation, effacement, or descent

The Cervix

- dilatation: latent phase: 0-4 cm (variable time); active phase: 4-10 cm
- effacement: thinning of the cervix by percentage or length of cervix (cm)
- consistency: firm vs. soft
- position: posterior vs. anterior
- application: contact between the cervix and presenting part (i.e. well or poorly applied)
  - see Bishop score (Table 22, OB38)

The Fetus

- fetal lie
  - orientation of the long axis of the fetus with respect to the long axis of the uterus (longitudinal, transverse, oblique)

- fetal presentation
  - fetal body part closest to the birth canal
    - breech (complete, frank, footling) (see Figure 5, OB23)
    - cephalic (vertex/occiput, face, asynclitic, brow)
    - transverse (shoulder)
  - compound (fetal extremity prolapses along with presenting part)
  - all except vertex are considered malpresentations (see Obstetrical Complications, OB16)

- fetal position
  - position of presenting part of the fetus relative to the maternal pelvis
    - OA: most common presentation (“normal”) – left OA most common
    - OP: most rotate spontaneously to OA; may cause prolonged second stage of labour
    - OT: leads to arrest of dilatation
  - normally, fetal head enters maternal pelvis and engages in OT position
  - subsequently rotates to OA position (or OP in a small percentage of cases)

- attitude
  - flexion/extension of fetal head relative to shoulders
    - brow presentation: head partially extended (requires C/S)
    - face presentation: head fully extended
      - mentum posterior always requires C/S, mentum anterior will deliver vaginally
• station
  - position of presenting part relative to ischial spines – determined by vaginal exam
    - at ischial spines = station 0 = engaged
    - -5 to -1 cm above ischial spines or
    - +1 to +5 cm below ischial spines
    - alternatively stations can be placed on a scale from -3 to +3

Four Stages of Labour

First Stage of Labour
• latent phase
  - uterine contractions typically infrequent and irregular
  - slow cervical dilatation (usually to 4 cm) and effacement
• active phase
  - rapid cervical dilatation to full dilatation (nulliparous ≥1.0 cm/h, multiparous ≥1.2 cm/h)
  - phase of maximum slope on cervical dilatation curve
  - painful, regular contractions q2-3min, lasting 45-60 s
  - contractions strongest at fundus, weakest at lower segment

Second Stage of Labour
• from full dilatation to delivery of the baby, duration varies based on parity, contraction quality, and type of analgesia
• mother feels a desire to bear down and push with each contraction
• women may choose a comfortable position that enhances pushing efforts and delivery
  - upright (semi-sitting, squatting) and LLDP are supported in the literature
• progress measured by descent

Third Stage of Labour
• from baby’s birth to separation and expulsion of the placenta
• can last up to 30 min before intervention indicated
• demonstrated by gush of fresh blood, umbilical cord lengthening, uterine fundus changing shape (firm and globular) and rising upward
• start oxytocin IV drip, or give 10 U IM or 5 mg IV push after delivery of anterior shoulder in anticipation of placental delivery, otherwise give after delivery of placenta
• routine oxytocin administration in third stage of labour can reduce the risk of PPH by >40%

Course of Normal Labour
<table>
<thead>
<tr>
<th>Stage</th>
<th>Nulliparous</th>
<th>Multiparous</th>
</tr>
</thead>
<tbody>
<tr>
<td>First</td>
<td>6-18 h</td>
<td>2-10 h</td>
</tr>
<tr>
<td>Second</td>
<td>30 min - 3 h</td>
<td>5-30 min</td>
</tr>
<tr>
<td>Third</td>
<td>5-30 min</td>
<td>5-30 min</td>
</tr>
</tbody>
</table>

Signs of Placental Separation
• Gush of blood
• Lengthening of cord
• Uterus becomes globular
• Fundus rises
Fourth Stage of Labour

- first postpartum hour
- monitor vital signs and bleeding, repair lacerations
- ensure uterus is contracted (palpate uterus and monitor uterine bleeding)
- inspect placenta for completeness and umbilical cord for presence of 2 arteries and 1 vein
- 3rd and 4th stages of labour most dangerous to the mother (i.e. hemorrhage)

The Cardinal Movements of the Fetus During Delivery

1. Head floating, before engagement
2. Engagement, descent, flexion
3. Further descent, internal rotation
4. Complete rotation, beginning extension
5. Complete extension
6. Restitution (external rotation)
7. Delivery of anterior shoulder
8. Delivery of posterior shoulder

Figure 7. Cardinal movements of fetus during delivery
Adapted from illustration in Williams Obstetrics, 19th ed

Analgesic and Anesthetic Techniques in Labour and Birth

- pain or anxiety leads to high endogenous catecholamines, which produce a direct inhibitory effect on uterine contractility

Non-Pharmacologic Pain Relief Techniques

- reduction of painful stimuli
  - maternal movement, position change, counter-pressure, abdominal compression
- activation of peripheral sensory receptors
  - superficial heat and cold
  - immersion in water during labour
  - touch and massage, acupuncture, and acupressure
  - TENS
  - intradermal injection of sterile water
  - aromatherapy
- enhancement of descending inhibitory pathways
  - attention focusing and distraction
  - hypnosis
  - music and audio analgesia
  - biofeedback

Pharmacologic Methods (see Anesthesia and Perioperative Medicine, A2)

- nitrous oxide (e.g. self-administered Entonox®)
- narcotics (usually combined with anti-emetic)
- pudendal nerve block
- perineal infiltration with local anesthetic
- regional anesthesia (epidural block, combined spinal-epidural, spinal)
**Fetal Monitoring in Labour**

- **see online Fetal Heart Rate Tutorial**

**Vaginal Exam**

- membrane status
- cervical effacement (thinning), dilatation, consistency, position, application
- fetal presenting part, position, station
- bony pelvis size and shape
- monitor progress of labour at regular intervals and document in a partogram

**Intrapartum Fetal Monitoring**

- intermittent fetal auscultation with Doppler device q15-30min for 1 min in first stage active phase following a contraction, q5min during second stage when pushing has begun
- continuous electronic FHR monitoring reserved for abnormal auscultation, prolonged labour, and labour which is induced or augmented, meconium present, multiple gestation/fetal complication
  - use of continuous electronic monitoring shown to lead to higher intervention rates and no improvement in outcome for the neonate when used routinely in all patients (ie no risk factors)
  - techniques for continuous monitoring include external (Doppler) vs. internal (fetal scalp electrode) monitoring
- fetal scalp sampling should be used in conjunction with electronic FHR monitoring and contraction monitoring (CTG) to resolve the interpretation of abnormal or atypical patterns

**Fetal Scalp Blood Sampling**

- cervix must be adequately dilated
- indicated when atypical or abnormal fetal heart rate is suggested by clinical parameters including heavy meconium or moderately to severely abnormal FHR patterns, including unexplained low variability, repetitive late decelerations, complex variable decelerations, fetal cardiac arrhythmias

Done by measuring pH or more recently fetal lactate
  - pH ≥7.25: normal, repeat if abnormal FHR persists
  - pH 7.21-7.24: repeat assessment in 30 min or consider delivery if rapid fall since last sample
  - pH ≤7.20: indicates fetal acidosis, delivery is indicated

- contraindications
  - known or suspected fetal blood dyscrasia (hemophilia, von Willebrand disease)
  - active maternal infection (HIV, genital herpes)

**Electronic FHR Monitoring**

- FHR measured by Doppler; contractions measured by tocometer
- described in terms of baseline FHR, variability (short-term, long-term), and periodicity (accelerations, decelerations)

- **Baseline FHR**
  - normal range is 110-160 bpm
  - parameter of fetal well-being vs. distress

- **Variability**
  - physiologic variability is a normal characteristic of FHR
  - variability is measured over a 15 min period and is described as: absent, minimal (<6 bpm), moderate (6-25 bpm), marked (>25 bpm)
  - normal variability indicates fetal acid-base status is acceptable
  - can only be assessed by electronic fetal monitoring (CTG)
  - variability decreases intermittently even in healthy fetus
  - see Table 19, OB36

- **Periodicity**
  - accelerations: increase of ≥15 bpm for ≥15 s, in response to fetal movement or uterine contraction (or ≥10 bpm for ≥10 s if <32 wk GA)
  - decelerations: 3 types, described in terms of shape, onset, depth, duration recovery, occurrence, and impact on baseline FHR and variability

**Approach to the Management of Abnormal FHR**

- **POISON – ER**
  - **P**osition (left lateral decubitus position)
  - **O**2 (100% by mask)
  - **I**V fluids (corrects maternal hypotension)
  - **F**etal scalp stimulation
  - **S**calp electrode
  - **C**hange maternal position
  - **O**xytocin
  - **N**otify MD
  - vaginal exam to rule out cord prolapse
  - rule out fever, dehydration, drug effects, prematurity
  - if above fails, consider C/S
Table 18. Factors Affecting Fetal Heart Rate

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Fetal Tachycardia (FHR &gt; 160 bpm)</th>
<th>Fetal Bradycardia (FHR &lt; 110 bpm)</th>
<th>Decreased Variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, hyperthermia, anemia, dehydration</td>
<td>Hypothermia, hypotension, hypoglycemia, position, umbilical cord occlusion</td>
<td>Infection, Dehydration</td>
<td></td>
</tr>
</tbody>
</table>

Fetal Factors
- Arrhythmia, anemia, infection, prolonged activity, chronic hypoxemia, congenital anomalies
- Rapid descent, dysrhythmia, heart block, hypoxia, vaginal stimulation (head compression), hypothermia, acidosis
- CNS anomalies
- Dyshytmia
- Inactivity/sleep cycle, preterm fetus

Drugs
- β-blockers
- Anesthetics
- Narcotics, sedatives
- Magnesium sulphate, β-blockers

Uteroplacental
- Early hypoxia (abruption, HTN)
- Late hypoxia (abruption, HTN)
- Acute cord prolapse
- Hypercontractility
- Hypoxia

Table 19. Comparison of Decelerations

Early Decelerations
- Uniform shape with onset early in contraction, returns to baseline by end of contraction, mirrors contraction (nadir occurs at peak of contraction)
- Gradual deceleration and return to baseline
- Often repetitive; no effect on baseline FHR or variability
- Benign, due to vagal response to head compression

Variable Decelerations
- Variable in shape, onset, and duration
- Most common type of periodicity seen during labour
- Often with abrupt drop in FHR >15 bpm below baseline (>15 s, <2 min); usually no effect on baseline FHR or variability
- Due to cord compression or, in second stage, forceful pushing with contractions

Complicated Variable Decelerations
- FHR drop <70 bpm for >60 s
- Loss of variability or decrease in baseline after deceleration
- Biphasic deceleration
- Slow return to baseline
- Baseline tachycardia or bradycardia
- May be associated with fetal academia

Late Decelerations
- Uniform shape with onset, nadir, and recovery occurring after peak of contraction, slow return to baseline
- May cause decreased variability and change in baseline FHR
- Due to fetal hypoxia and acidemia, maternal hypotension, or uterine hypertonus
- Usually a sign of uteroplacental insufficiency (an ominous sign)

Table 20. Classification of Intrapartum EFM Tracings

<table>
<thead>
<tr>
<th>Normal Tracing (Category 1)</th>
<th>Atypical Tracing* (Category 2)</th>
<th>Abnormal Tracing* (Category 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline 110-160 bpm</td>
<td>Bradycardia 100-110 bpm</td>
<td>Bradycardia &lt;100 bpm</td>
</tr>
<tr>
<td>Tachycardia &gt;160 bpm</td>
<td>Tachycardia &gt;160 bpm for &gt;30-80 min</td>
<td>Tachycardia &gt;160 bpm for &gt;80 min</td>
</tr>
<tr>
<td>Rising baseline</td>
<td>Rising baseline</td>
<td>Erratic baseline</td>
</tr>
</tbody>
</table>

Variability
- 6-25 bpm for <40 min
- ≤5 bpm for 40-80 min
- <5 bpm for >80 min
- ≥25 bpm for >10 min
Table 20. Classification of Intrapartum EFM Tracings (continued)

<table>
<thead>
<tr>
<th>Decelerations</th>
<th>Normal Tracing (Category 1)</th>
<th>Atypical Tracing* (Category 2)</th>
<th>Abnormal Tracing* (Category 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Early decelerations</td>
<td>Repetitive ((\geq 3)) uncomplicated variable decelerations</td>
<td>Repetitive ((\geq 3)) complicated variable decelerations</td>
</tr>
<tr>
<td>Early decelerations</td>
<td>Occasional uncomplicated variable decelerations</td>
<td>Occasional late decelerations</td>
<td>Repetitive late decelerations</td>
</tr>
<tr>
<td>Occasional late decelerations</td>
<td></td>
<td>Any prolonged deceleration (2-3 min)</td>
<td>Any prolonged deceleration ((\geq 3) min)</td>
</tr>
</tbody>
</table>

| Accelerations                   | Accelerations spontaneous or during scalp stimulation | Absent with scalp stimulation | Nearly absent |

| Action                          | EFM may be interrupted for \(\leq 30\) min if mother/fetus stable | Further assessment required | Action required: review clinical situation, obtain scalp pH, prepare for possible delivery |

Adapted from SOGC Guidelines, September 2008

*Previous classification was “reassuring” vs. “non-reassuring”, but distinction is now made between tracings that have some concerning changes but do not require immediate action (atypical) versus those with major concerns requiring immediate intervention (abnormal)

Fetal Oxygenation
- uterine contractions during labour decrease uteroplacental blood flow, which results in reduced oxygen delivery to the fetus
- most fetuses tolerate this reduction in flow and have no adverse effects
- distribution of oxygen to the fetus depends on maternal, uteroplacental, and fetal factors
- fetal response to hypoxia/asphyxia:
  - decreased movement, tone, and breathing activities
  - anaerobic metabolism (decreased pH)
  - transient fetal bradycardia followed by fetal tachycardia
  - redistribution of fetal blood flow
    - increased flow to brain, heart, and adrenals
    - decreased flow to kidneys, lungs, gut, liver, and peripheral tissues
    - increase in blood pressure

Table 21. Factors Affecting Fetal Oxygenation

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mechanism</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal</td>
<td>Decreased maternal oxygen carrying capacity</td>
<td>Significant anemia (iron deficiency, hemoglobinopathies), carboxyhemoglobin (smokers)</td>
</tr>
<tr>
<td></td>
<td>Decreased uterine blood flow</td>
<td>Hypotension (blood loss, sepsis), regional anesthesia, maternal positioning</td>
</tr>
<tr>
<td></td>
<td>Chronic maternal conditions</td>
<td>Vasculopathies (SLE, type 1 DM, chronic HTN, antiphospholipid syndrome, cyanotic heart disease, COPD)</td>
</tr>
<tr>
<td>Uteroplacental</td>
<td>Uterine hypertonus</td>
<td>Placental abruption, hyperstimulation secondary to oxytocin, prostaglandins, or normal labour</td>
</tr>
<tr>
<td></td>
<td>Uteroplacental dysfunction</td>
<td>Placental abruption, placental infarction (dysfunction marked by IUGR, oligohydramnios, abnormal Doppler studies), chorioamnionitis, placental edema (DM, hydrops), placental senescence (post-dates)</td>
</tr>
<tr>
<td>Fetal</td>
<td>Cord compression</td>
<td>Oligohydramnios, cord prolapse, or entanglement</td>
</tr>
<tr>
<td></td>
<td>Decreased fetal oxygen carrying capacity</td>
<td>Significant anemia (isoimmunization, feto-maternal bleed), carboxyhemoglobin (exposure to smokers)</td>
</tr>
</tbody>
</table>

### Induction of Labour

**Definition**
- artificial initiation of labour in a pregnant woman prior to spontaneous initiation to deliver the fetus and placenta

**Prerequisites for Labour Induction**
- capability for C/S if necessary
- maternal
  - short, thin, soft, anterior cervix with open os (“inducible” or “ripe”)
  - if cervix is not ripe, use prostaglandin vaginal insert (Cervidil®), prostaglandin gel (Prevadin®), or Foley catheter
- fetal
  - normal fetal heart tracing
  - cephalic presentation
  - adequate fetal monitoring available

Induction is indicated when the risk of continuing pregnancy exceeds the risks associated with induced labour and delivery
• likelihood of success determined by Bishop score
  ▪ cervix considered unfavourable if <6
  ▪ cervix favourable if ≥6
  ▪ score of 9-13 associated with high likelihood of vaginal delivery

<table>
<thead>
<tr>
<th>Cervical Characteristic</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Position</td>
<td>Posterior</td>
<td>Mid</td>
<td>Anterior</td>
<td>–</td>
</tr>
<tr>
<td>Consistency</td>
<td>Firm</td>
<td>Medium</td>
<td>Soft</td>
<td>–</td>
</tr>
<tr>
<td>Effacement (%)</td>
<td>0-30</td>
<td>40-50</td>
<td>60-70</td>
<td>≥80</td>
</tr>
<tr>
<td>Dilatation (cm)</td>
<td>0</td>
<td>1-2</td>
<td>3-4</td>
<td>≥5</td>
</tr>
<tr>
<td>Station of Fetal Head</td>
<td>-3</td>
<td>-2</td>
<td>-1, 0</td>
<td>+1, +2, +3</td>
</tr>
</tbody>
</table>

**Table 22. Bishop Score**

**Indications**

- post-dates pregnancy (generally >41 wk) = most common reason for induction
- maternal factors
  ▪ DM = second most common reason for induction
  ▪ gestational HTN
  ▪ other maternal medical problems, e.g. renal or lung disease, chronic hypertension, cholestasis or pregnancy
  ▪ maternal age over 40
- maternal-fetal factors
  ▪ isoimmunization, PROM, chorioamnionitis, post-term pregnancy
- fetal factors
  ▪ suspected fetal jeopardy as evidenced by biochemical or biophysical indications
  ▪ fetal demise. IUGR, oligo/polyhydraminos, anomalies requiring surgical intervention, twins
  ▪ previous still birth, low PAPP-A

**Risks**

- failure to achieve labour and/or vaginal birth
- uterine hyperstimulation with fetal compromise or uterine rupture
- maternal side effects to medications
- uterine atony and PPH

**Contraindications**

- maternal
  ▪ prior classical or inverted T-incision C/S or uterine surgery (e.g. myomectomy)
  ▪ unstable maternal condition
  ▪ active maternal genital herpes
  ▪ invasive cervical carcinoma
  ▪ pelvic structure deformities
- maternal-fetal
  ▪ placenta previa or vasa previa
  ▪ cord presentation
- fetal
  ▪ fetal distress, malpresentation /abnormal lie, preterm fetus without lung maturity

**Induction Methods**

**CERVICAL RIPENING**

**Definition**

- use of medications or other means to soften, efface, and dilate the cervix, increases likelihood of successful induction
- ripening of an unfavourable cervix (Bishop score <6) is warranted prior to induction of labour

**Methods**

- intravaginal prostaglandin PGE2 gel (Prostin® gel): long and closed cervix
  ▪ recommended dosing interval of prostaglandin gel is every 6 to 12 h up to 3 doses
- intravaginal PGE2 (Cervidil®): long and closed cervix, may use if ROM
  ▪ continuous release, can be removed if needed
  ▪ controlled release PGE2
- Foley catheter placement to mechanically dilate the cervix
INDUCTION OF LABOUR

Amniotomy
• artificial rupture of membranes (amniotomy) to stimulate prostaglandin synthesis and secretion; may try this as initial measure if cervix is open and soft, the membranes can be felt, and if the head is present at the cervix
• few studies address the value of amniotomy alone for induction of labour
• amniotomy plus intravenous oxytocin: more women delivered vaginally at 24 h than amniotomy alone (relative risk = 0.03) and had fewer instrumental vaginal deliveries (relative risk = 5.5)

Oxytocin
• oxytocin (Pitocin®): 10 U in 1L NS, run at 0.5-2 mU/min IV increasing by 1-2 mU/min q20-60min to a max of 36-48 mU/min
  ▪ reduces rate of unsuccessful vaginal deliveries within 24 h when used alone (8.3% vs. 54%, RR 0.16)
  ▪ ideal dosing regime of oxytocin is not known
  ▪ current recommendations: use the minimum dose to achieve active labour and increase q30min as needed
  ▪ reassessment should occur once a dose of 20 mU/min is reached
• potential complications
  ▪ hyperstimulation/tetanic contraction (may cause fetal distress or rupture of uterus)
  ▪ uterine muscle fatigue, uterine atony (may result in PPH)
  ▪ vasopressin-like action causing anti-diuresis

Augmentation of Labour
• augmentation of labour is used to promote adequate contractions when spontaneous contractions are inadequate and cervical dilatation or descent of fetus fails to occur
• oxytocin (0.5-2 mU/min IV increasing by 1-2 mU/min q20-60min to a max of 36-48 mU/min)

Abnormalities and Complications of Labour and Delivery

Meconium in Amniotic Fluid

Epidemiology
• present early in labour in 10% of pregnancies
• in general, meconium may be present in up to 25% of all labours; usually NOT associated with poor outcome, but extra care is required at time of delivery to avoid aspiration. Concern is fluid changes from clear to meconium stained. Always abnormal if seen in preterm patient

Etiology
• likely cord compression ± uterine hypertonia
• may indicate undiagnosed breech
• increasing meconium during labour may be a sign of fetal distress

Features
• may be watery or thicker
• light yellow/green or dark green-black in colour

Treatment
• call respiratory therapy, neonatology, or pediatrics to delivery room
• oropharynx suctioning upon head expulsion or immediately after delivery if baby not breathing spontaneously (do NOT stimulate infant before)
• consider amnioinfusion of ~800 mL of IV NS over 50-80 min during active stage of labour and a maintenance dose of ~3 mL/min until delivery
• closely monitor FHR for signs of fetal distress
Abnormal Progression of Labour (Dystocia)

**Definition**
- expected patterns of descent of the presenting part and cervical dilatation fail to occur in the appropriate time frame; can occur in all stages of labour
- during active phase: >4 h of <0.5 cm/h
- during 2nd phase: >1 h with no descent during active pushing

**Etiology**
- **Power** (leading cause): contractions (hypotonic, incoordinate), inadequate maternal expulsive efforts
- **Passenger**: fetal position, attitude, size, anomalies (hydrocephalus)
- **Passage**: pelvic structure (CPD), maternal soft tissue factors (tumours, full bladder or rectum, vaginal septum)
- **Psyche**: hormones released in response to stress may contribute to dystocia; psychological and physiological stress should be evaluated as part of the management once dystocia has been diagnosed

**Management**
- confirm diagnosis of labour (rule out false labour)
- search for factors of CPD
- diagnosed if adequate contractions measured by intrauterine pressure catheter (IUPC) with no descent/dilatation for >2 h
- management: if CPD ruled out, IV oxytocin augmentation ± amniotomy

**Risks of Dystocia**
- inadequate progression of labour is associated with an increased incidence of:
  - maternal stress
  - maternal infection
  - postpartum hemorrhage
  - need for neonatal resuscitation
  - fetal compromise (from uterine hyperstimulation)
  - uterine rupture
  - hypotension

Shoulder Dystocia

**Definition**
- fetal anterior shoulder impacted above symphysis pubis after fetal head has been delivered
- life threatening emergency

**Etiology/Epidemiology**
- incidence 0.15-1.4% of deliveries
- occurs when breadth of shoulders is greater than biparietal diameter of the head

**Risk Factors**
- maternal: obesity, DM, multiparity, previous shoulder dystocia
- fetal: prolonged gestation, macrosomia
- labour
  - prolonged 2nd stage
  - instrumental midpelvic delivery

**Clinical Features**
- "turtle sign": head delivered but retracts against inferior portion of pubic symphysis
- complications
  - fetal:
    - hypoxic ischemic encephalopathy (chest compression by vagina or cord compression by pelvis can lead to hypoxia)
    - brachial plexus injury (Erb’s palsy: C5-C7; Klumpke’s palsy: C8-T1), 90% resolve within 6 mo
    - fracture (clavicle, humerus, cervical spine)
    - death
  - maternal:
    - perineal injury
    - PPH (uterine atony, lacerations)
    - uterine rupture

**Treatment**
- goal: to displace anterior shoulder from behind symphysis pubis; follow a stepwise approach of maneuvers until goal achieved
• other options
  - cleidotomy (deliberate fracture of neonatal clavicle)
  - Zavanelli maneuver: replacement of fetus into uterine cavity and emergent C/S
  - symphysiotomy

Prognosis
• 1% risk of long-term disability for infant

### Umbilical Cord Prolapse

**Definition**
• descent of the cord to a level adjacent to or below the presenting part, causing cord compression between presenting part and pelvis

**Etiology/Epidemiology**
• increased incidence with prematurity/PROM, fetal malpresentation (~50% of cases), low-lying placenta, polyhydramnios, multiple gestation, CPD
• incidence: 1/200 – 1/400 deliveries

**Clinical Features**
• visible or palpable cord
• FHR changes (variable decelerations, bradycardia, or both)

**Treatment**
• emergency C/S
• O2 to mother, monitor fetal heart
• alleviate pressure of the presenting part on the cord by placing digit in vagina (maintain this position until C/S)
• keep cord warm and moist by replacing it into the vagina ± applying warm saline soaks
• roll mom onto all fours
• position mother in Trendelenburg or knee-to-chest position
• if fetal demise or too premature (<22 wk), allow labour and delivery

### Uterine Rupture

**Etiology/Epidemiology**
• associated with previous uterine scar (in 40% of cases), hyperstimulation with oxytocin, grand multiparity, and previous intrauterine manipulation
• generally occurs during labour, but can occur earlier with a classical incision
• 0.5-0.8% incidence, up to 12% with classical incision

**Clinical Features**
• prolonged fetal bradycardia – most common presentation
• acute onset of constant lower abdominal pain, may not have pain if receiving epidural analgesia
• hyper or hypotonic uterine contractions
• vaginal bleeding
• intra-abdominal hemorrhage

**Risk Factors**
• uterine scarring (i.e. previous uterine surgeries including Cesarean, perforation with D&C, myomectomy)
• excessive uterine stimulation (i.e. protracted labour, oxytocin, prostaglandins)
• uterine trauma (i.e. operative equipment, ECV)
• multiparity
• uterine abnormalities
• placenta accreta

**Treatment**
• rule out placental abruption
• immediate delivery for fetal survival
• maternal stabilization (may require hysterectomy), treat hypovolemia

**Complications**
• maternal mortality 1-10%
• maternal hemorrhage, shock, DIC
• amniotic fluid embolus
• hysterectomy if uncontrollable hemorrhage
• fetal distress, associated with 50% fetal mortality

*In Canada (2013), lifetime risk of maternal death is 1 in 5,200
Amniotic Fluid Embolus

**Definition**
- amniotic fluid debris in maternal circulation triggering an anaphylactoid immunologic response

**Etiology/Epidemiology**
- rare intrapartum or immediate postpartum complication
- 60-80% maternal mortality rate, accounts for 10% of all maternal deaths
- leading cause of maternal death in induced abortions and miscarriages
- 1/8,000-1/80,000 births

**Risk Factors**
- placental abruption
- rapid labour
- multiparity
- uterine rupture
- uterine manipulation

**Differential Diagnosis**
- pulmonary embolus, drug-induced anaphylaxis, septic shock, eclampsia, HELLP syndrome, abruption, chronic coagulopathy

**Clinical Features**
- sudden onset of respiratory distress, cardiovascular collapse (hypotension, hypoxia), and coagulopathy
- seizure in 10%
- ARDS and left ventricular dysfunction seen in survivors

**Management**
- supportive measures (high flow O₂, ventilation support, fluid resuscitation, inotropic support, ± intubation), coagulopathy correction
- ICU admission

Chorioamnionitis

**Definition**
- infection of the chorion, amnion, and amniotic fluid typically due to ascending infection by organisms of normal vaginal flora

**Etiology/Epidemiology**
- incidence 1-5% of term pregnancies and up to 25% in preterm deliveries
- ascending from vagina
- predominant microorganisms include: GBS, *Bacteroides* and *Prevotella* species, *E. coli*, and anaerobic *Streptococcus*

**Risk Factors**
- prolonged ROM, long labour, multiple vaginal exams during labour, internal monitoring
- bacterial vaginosis and other vaginal infections

**Clinical Features**
- maternal fever, maternal or fetal tachycardia, uterine tenderness, foul, and purulent cervical discharge

**Investigations**
- CBC: leukocytosis
- amniotic fluid: leukocytes or bacteria

**Treatment**
- IV antibiotics
  - ampicillin (2 g IV q6h) and gentamicin (1.5 mg/kg q8h)
  - anaerobic coverage (i.e. clindamycin if C/S)
- expedient delivery regardless of gestational age

**Complications**
- bacteremia of mother or fetus, wound infection if C/S, pelvic abscess, infant meningitis
Operative Obstetrics

Operative Vaginal Delivery

Definition
• forceps or vacuum extraction

Indications
• fetal
  ▪ atypical or abnormal fetal heart rate tracing, evidence of fetal compromise
  ▪ consider if second stage is prolonged as this may be due to poor contractions or failure of fetal head to rotate
• maternal
  ▪ need to avoid voluntary expulsive effort (e.g. cardiac/cerebrovascular disease)
  ▪ exhaustion, lack of cooperation, and excessive analgesia may impair pushing effort

Contraindications
• non-cephalic presentation
• unengaged head
• cervix incompletely dilated

Forceps

Outlet Forceps Position
• head visible between labia in between contractions
• sagittal suture in or close to AP diameter
• rotation cannot exceed 45°

Low Forceps Position
• presenting part at station +2 or greater
• subdivided based on whether rotation less than or greater than 45 degrees

Mid Forceps Position
• presenting part below spines but above station +2

Types of Forceps
• Simpson or Tucker-McLane forceps for OA presentations
• Kielland (rotational) forceps when rotation of head is required
• Piper forceps for breech

Vacuum Extraction
• traction instrument used as alternative to forceps delivery; aids maternal pushing
• contraindications: <34 wk GA, fetal head deflexed, fetus requires rotation, fetal condition (e.g. bleeding disorder)

Table 23. Advantages and Disadvantages of Forceps versus Vacuum Extraction

<table>
<thead>
<tr>
<th>Advantage (Forceps)</th>
<th>Advantage (Vacuum Extraction)</th>
<th>Disadvantage (Forceps)</th>
<th>Disadvantage (Vacuum Extraction)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher overall success rate for vaginal delivery</td>
<td>Easier to apply</td>
<td>Greater incidence of maternal injury</td>
<td>Contraindicated if fetus at risk for coagulation defect</td>
</tr>
<tr>
<td>Decreased incidence of fetal morbidity</td>
<td>Less anesthesia required</td>
<td>Suitable only for vertex presentations</td>
<td>Maternal pushing required</td>
</tr>
<tr>
<td></td>
<td>Less maternal soft-tissue injury compared to forceps</td>
<td>Maternal pushing required</td>
<td>Contraindicated in preterm delivery</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal: anesthesia risk, lacerations, injury to bladder, uterus, or bone, pelvic nerve damage, PPH, infections</td>
<td>Increased incidence of cephalohematoma and retinal hemorrhages compared to forceps</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fetal: fractures, facial nerve palsy, trauma to face/</td>
<td>Subgaleal hemorrhage, Subaponeurotic hemorrhage,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scalp, intracerebral hemorrhage, cephalohematoma, cord compression</td>
<td>Soft tissue trauma</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Limit for Trial of Vacuum
• After 3 pulls over 3 contractions with no progress
• After 3 pop-offs with no obvious cause
• 20 min and delivery is not imminent
Lacerations
- first degree: involves skin and vaginal mucosa but not underlying fascia and muscle
- second degree: involves fascia and muscles of the perineal body but not the anal sphincter
- third degree: involves the anal sphincter but does not extend through it
- fourth degree: extends through the anal sphincter into the rectal mucosa

Episiotomy
Definition
- incision in the perineal body at the time of delivery
- essentially a controlled second degree laceration
- midline: incision through central tendinous portion of perineal body and insertions of superficial transverse perineal and bulbocavernous muscle
  - heals better, but increases risk of 3\(\frac{3}{4}\)th degree tears
- mediolateral: incision through bulbocavernous, superficial transverse perineal muscle, and levator ani
  - reduced risk of extensive tear but more painful
  - easier to repair

Indications
- to relieve obstruction of the unyielding perineum
- instrumental delivery
- controversial between practitioners as to whether it is preferable to make a cut or let the perineum tear as needed
- current evidence suggests letting perineum tear and then repair as needed (restricted use)

Complications
- infection, hematoma, extension into anal musculature or rectal mucosa, fistula formation, incontinence

Cesarean Delivery
Epidemiology
- incidence 20-25%

Indications
- maternal: obstruction, active herpetic lesion on vulva, invasive cervical cancer, previous uterine surgery (past C/S is most common), underlying maternal illness (eclampsia, HELLP syndrome, heart disease)
- maternal-fetal: failure to progress, placental abruption or previa, vasa previa
- fetal: abnormal fetal heart tracing, malpresentation, cord prolapse, certain congenital anomalies

Types of Cesarean Incisions
- skin
  - transverse (i.e. Pfannensteil)
  - decreased exposure and slower entry
  - improved strength and cosmesis
- vertical midline
  - rapid peritoneal entry and increased exposure
  - increased dehiscence
- uterine
  - low transverse (most common): in noncontractile segment
  - decreased chance for rupture in subsequent pregnancies
- low vertical
  - used for very preterm infants, poorly developed maternal lower uterine segment
  - classical (rare): in thick, contractile segment
  - used for transverse lie, fetal anomaly, >2 fetuses, lower segment adhesions, obstructing fibroid, morbidly obese patients

Risks/Complications
- anesthesia
- hemorrhage (average blood loss ~1,000 cc)
- infection (UTI, wound, endometritis)
  - single dose prophylactic antibiotic should be used (e.g. cefazolin 1-2 g)
- injury to surrounding structures (bowel, bladder, ureter, uterus)
- thromboembolism (DVT, PE)
- increased recovery time/hospital stay
- maternal mortality (<0.1%)

Muscles of Perineal Body
- Superficial transverse perineal
- Bulbocavernous
- External anal sphincter

Risk Factors for Primary and Subsequent Anal Sphincter Lacerations
Am J Obstet Gynecol 2007;196:344
Objective: Assess effects of pregnancy, delivery, and parity on risk of primary and secondary anal sphincter laceration in women with 1st vaginal delivery (VD), VBAC, or 2nd VD.
Methods: Retrospective cohort study of all deliveries at one hospital from 1995-2002.
Conclusion: 20,074 live singleton deliveries were included. Women with first VD and VBAC both had OR 5.1 for laceration compared to 2nd VD. Forceps and midline episiotomy significantly increased risk of laceration for all 3 groups. Second stage of labor >2 h only increased risk for 1st VD. Factors that had no significant increase in risk: infant birth weight >3,500 g and vacuum delivery. Women with prior anal sphincter laceration are at 3x increased risk for subsequent sphincter laceration, compared with women with prior vaginal delivery without sphincter laceration.

Restrictive vs. Routine Episiotomies with Vaginal Births
Cochrane DB Syst Rev 2009;1:CD000081
Study: This systematic review and meta-analysis of 8 RCTs assessed the effects of restrictive (only done for fetal indications or if severe perineal trauma was judged to be imminent) and routine (liberally done to prevent any tear) use of episiotomy during vaginal birth.
Patients: Of the 2,709 patients in the routine episiotomy group, 2,035 (75%) women had episiotomies. In the restrictive episiotomy group, 776 (28%) of the 2,733 women had episiotomies. The restrictive episiotomy group, 776 (28%) of the 2,733 women had episiotomies.
Results: Restrictive episiotomies appear to have less severe perineal trauma (RR 0.67), less suturing (RR 0.71), and fewer healing complications at 7 d (RR 0.69) compared to routine episiotomies. There is no difference for pain measures, dyspareunia, urinary incontinence, and severe vaginal or perineal trauma, but there was an increased risk of anterior perineal trauma (RR 1.84) with restrictive episiotomy. Similar results were obtained when comparing restrictive versus routine mediolateral versus midline episiotomy.
Conclusions: Compared to routine use, restrictive use of episiotomy during vaginal delivery appears to be more beneficial.

Common OR Questions
7 Layers to Dissect
Skin, fatty layer, fascia, muscle separation (rectus abdominis), peritoneum, bladder flap, uterus

Layers of the Rectus Sheath
Above the arcuate line: external oblique, internal oblique, rectus abdominis, internal oblique, transversus abdominis
Below the arcuate line: external oblique, internal oblique, transversus abdominis, rectus abdominis

Name of the Obliterated Umbilical Ligament
Urachus
Vaginal Birth After Cesarean (Trial of Labour After Cesarean)

- recommended after previous low transverse incision
- success rate varies with indication for previous C/S (generally 60-80%)
- risk of uterine rupture (<1% with low transverse incision)

Contraindications
- previous classical, inverted T, or unknown uterine incision, or complete transection of uterus (6% risk of rupture)
- history of uterine surgery (e.g. myomectomy) or previous uterine rupture
- multiple gestation
- non-vertex presentation or placenta previa
- inadequate facilities or personnel for emergency C/S

Puerperal Complications

- puerperium: 6 wk period of adjustment after pregnancy when pregnancy-induced anatomic and physiologic changes are reversed

Postpartum Hemorrhage

Definition
- loss of >500 mL of blood at the time of vaginal delivery, or >1,000 mL with C/S
- early (immediate) – within first 24 h postpartum
- late (delayed) – after 24 h but within first 6 wk

Epidemiology
- incidence 5-15%

Etiology (4 Ts)
1. Tone
   - uterine atony
     - most common cause of PPH
     - avoid by giving oxytocin with delivery of the anterior shoulder or placenta
     - occurs within first 24 h
   - due to
     - overdistended uterus (polyhydramnios, multiple gestations, macrosomia)
     - uterine muscle exhaustion (prolonged or rapid labour, grand multiparity, oxytocin use, general anaesthetic)
     - uterine distortion (fibroids, placenta previa, placental abruption)
     - intra-amniotic infection (fever, prolonged ROM)

2. Tissue
   - retained placental products (membranes, cotyledon or succenturiate lobe)
   - retained blood clots in an atonic uterus
   - gestational trophoblastic neoplasia
   - abnormal placentation

3. Trauma
   - laceration (vagina, cervix, uterus), episiotomy, hematoma (vaginal, vulvar, retroperitoneal), uterine rupture, uterine inversion

4. Thrombin
   - coagulopathy (pre-existing or acquired)
     - most identified prior to delivery (low platelets increases risk)
     - includes hemophilia, DIC, Aspirin use, ITP, TTP, vWD (most common)
     - therapeutic anti-coagulation

Investigations
- assess degree of blood loss and shock by clinical exam
- explore uterus and lower genital tract for evidence of tone, tissue, or trauma
- may be helpful to observe red-topped tube of blood – no clot in 7-10 min indicates coagulation problem

Management
- ABCs, call for help
- 2 large bore IVs, run crystalloids wide open
- CBC, coagulation profile, cross and type 4 units pRBCs
- treat underlying cause
- Foley catheter to empty bladder and monitor urine output

Uterine atony is the most common cause of PPH

DDx of Early PPH – 4 Ts
- Tone (atony)
- Tissue (retained placenta, clots)
- Trauma (laceration, inversion)
- Thrombin (coagulopathy)

DDx of Late PPH
- Retained products ± endometritis
- Sub-involution of uterus
Medical Therapy
- oxytocin 5U IV bolus with delivery of anterior shoulder
  - 20–40 U/250 mL in crystalloid
  - in addition can give 10 U IM if CV collapse or IV access not possible
- methylergonovine maleate (ergotamine) 0.25 mg IM/IMM q5min up to 1.25 mg; can be given as IV bolus of 0.125 mg (may exacerbate HTN)
- carboprost (Hemabate®), a synthetic PGF-1α analog 250 µg IM/IMM q15min to max 2 mg (major prostaglandin side effects and contraindicated in cardiovascular, pulmonary, renal, and hepatic dysfunction)
- misoprostol 600–800 µg po/sl (faster) or pr/pv (side effect: pyrexia if >600 µg)
- tranexamic acid (Cyklokapron®) 1 g IV, an antifibrinolytic

Local Control
- bimanual compression: elevate the uterus and massage through patient’s abdomen
- uterine packing (mesh with antibiotic treatment)
- Bakri Balloon for tamponade: may slow hemorrhage enough to allow time for correction of coagulopathy or for preparation of an OR

Surgical Therapy (Intractable PPH)
- D&C (beware of vigorous scraping which can lead to Asherman's syndrome)
- embolization of uterine artery or internal iliac artery by interventional radiologist
- laparotomy with bilateral ligation of uterine artery (may be effective), internal iliac artery (not proven), ovarian artery, or hypogastric artery
- hysterectomy last option with angiographic embolization if post-hysterectomy bleeding

Retained Placenta

Definition
- placenta undelivered after 30 min postpartum

Etiology
- placenta separated but not delivered
- abnormal placental implantation (placenta accreta, placenta increta, placenta percreta)

Risk Factors
- placenta previa, prior C/S, post-pregnancy curettage, prior manual placental removal, uterine infection

Clinical Features
- risk of postpartum hemorrhage and infection

Investigations
- explore uterus
- assess degree of blood loss

Management
- 2 large bore IVs, type and screen
- Brant maneuver (firm traction on umbilical cord with one hand applying suprapubic pressure to avoid uterine inversion by holding uterus in place)
- oxytocin 10 IU in 20 mL NS into umbilical vein
- manual removal if above fails
- D&C if required

Uterine Inversion

Definition
- inversion of the uterus through cervix ± vaginal introitus

Etiology/Epidemiology
- often iatrogenic (excess cord traction with fundal placenta)
- excessive use of uterine tocolytics
- more common in grand multiparous (lax uterine ligaments)
- 1/1,500–1/2,000 deliveries

Clinical Features
- can cause profound vasovagal response with bradycardia, vasodilation, and hypovolemic shock
- shock may be disproportionate to maternal blood loss
Management
• urgent management essential, call anesthesia
• ABCs: initiate IV crystalloids
• can use tocolytic drug (see ‘Management’ of Preterm Labour, OB16) or nitroglycerin IV to relax uterus and aid replacement
• replace uterus without removing placenta
• remove placenta manually and withdraw slowly
• IV oxytocin infusion (only after uterus replaced)
• re-explore uterus
• may require general anesthetic ± laparotomy

Postpartum Pyrexia

Definition
• fever >38°C on any 2 of the first 10 d postpartum, except the first day

Etiology
• endometritis
• wound infection (check C/S and episiotomy sites)
• mastitis/engorgement
• UTI
• atelectasis
• pneumonia
• DVT, pelvic thrombophlebitis

Investigations
• detailed history and physical exam, relevant cultures
• for endometritis: blood and genital cultures

Treatment
• depends on etiology
  ▪ infection: empiric antibiotics, adjust when sensitivities available
    • endometritis: clindamycin + gentamycin IV
    • mastitis: cloxacillin or cephalaxin
    • wound infection: cephalaxin, frequent sitz baths for episiotomy site infection
  ▪ DVT: anticoagulants
• prophylaxis against post-C/S endometritis: begin antibiotic immediately after cord clamping and administer only 1-3 doses – cefazolin is most common choice

ENDOMETRITIS
• definition: infection of uterine myometrium and parametrium
• clinical features: fever, chills, abdominal pain, uterine tenderness, foul-smelling discharge, or lochia
• treatment: depends on infection severity; oral antibiotics if well, IV with hospitalization in moderate to severe cases

VENOUS THROMBOEMBOLISM
• see Venous Thromboembolism, OB31

Mastitis
• definition: inflammation of mammary glands
• must rule out inflammatory carcinoma, as indicated
• differentiate from mammary duct ectasia: mammary duct(s) beneath nipple clogged and dilated ± ductal inflammation ± nipple discharge (thick, grey to green), often postmenopausal women
Table 24. Lactational vs. Non-Lactational Mastitis

<table>
<thead>
<tr>
<th></th>
<th>Lactational</th>
<th>Non-Lactational</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Epidemiology</strong></td>
<td>More common than non-lactational</td>
<td>Periductal mastitis most common</td>
</tr>
<tr>
<td></td>
<td>Often 2-3 wk postpartum</td>
<td>Mean age 32 yr</td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>S. aureus</td>
<td>May be sterile</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be infected with S. aureus or other anaerobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Smoking is risk factor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be associated with mammary duct ectasia</td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Unilateral localized pain</td>
<td>Subareolar pain</td>
</tr>
<tr>
<td></td>
<td>Tenderness</td>
<td>May have subareolar mass</td>
</tr>
<tr>
<td></td>
<td>Erythema</td>
<td>Discharge (variable colour)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nipple inversion</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Heat or ice packs</td>
<td>Broad-spectrum antibiotics and I&amp;D</td>
</tr>
<tr>
<td></td>
<td>Continued nursing/pumping</td>
<td>Total duct excision (definitive)</td>
</tr>
<tr>
<td></td>
<td>Antibiotics (cloxacillin/cephalexin)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Erythromycin if pen-allergic)</td>
<td></td>
</tr>
<tr>
<td><strong>Abscess</strong></td>
<td>Fluidant mass</td>
<td>If mass does not resolve, FNA to exclude cancer and U/S to assess presence of abscess</td>
</tr>
<tr>
<td></td>
<td>Purulent nipple discharge</td>
<td>Treatment includes antibiotics, aspiration, or I&amp;D (tends to recur)</td>
</tr>
<tr>
<td></td>
<td>Fever, leukocytosis</td>
<td>May develop mammary duct fistula</td>
</tr>
<tr>
<td></td>
<td>Discontinue nursing, IV antibiotics (nafcillin/oxacillin), I&amp;D usually required</td>
<td>A minority of non-lactational abscesses may occur peripherally in breast with no associated periductal mastitis (usually S. aureus)</td>
</tr>
</tbody>
</table>

Postpartum Mood Alterations

**POSTPARTUM BLUES**
- 40-80% of new mothers, onset day 3-10; extension of the “normal” hormonal changes and adjustment to a new baby
- self-limited, should resolve by 2 wk
- manifested by mood lability, depressed affect, increased sensitivity to criticism, tearfulness, fatigue, irritability, poor concentration/despondency, anxiety, insomnia

**POSTPARTUM DEPRESSION**
- definition: major depression occurring in a woman within 6 mo of childbirth (see Psychiatry, PS12)
- epidemiology: 10-15%, risk of recurrence 50%
- risk factors
  - personal or family history of depression (including PPD)
  - prenatal depression or anxiety
  - stressful life situation
  - poor support system
  - unwanted pregnancy
  - colicky or sick infant
- clinical features: suspect if the “blues” last beyond 2 wk, or if the symptoms in the first 2 wk are severe (e.g. extreme disinterest in the baby, suicidal or homicidal/infanticidal ideation)
- assessment: Edinburgh Postnatal Depression Scale or other
- treatment: antidepressants, psychotherapy, supportive care, ECT if refractory
- prognosis: interferes with bonding and attachment between mother and baby so it can have long-term effects

**POSTPARTUM PSYCHOsis**
- definition: onset of psychotic symptoms over 24-72 h within first month postpartum, can present in the context of depression
- epidemiology: rare (0.2%)
Postpartum Care

Postpartum Office Visit at 6 Weeks

Care of Mother (The 10 Bs)
- Be careful: do not use douches or tampons for 4-6 wk post-delivery
- Be fit: encourage gradual increases in walking, Kegel exercises
- Birth control: assess for use of contraceptives; breastfeeding is NOT an effective method of birth control (see Gynecology, GY18, for more detail about different contraceptive options postpartum)
- Bladder: assess for urinary incontinence, maintain high fluid intake
- Blood pressure: especially if gestational HTN
- Blood tests: glucose, CBC (for anemia as sign of hematomas, retained placenta)
- Blues: (see Postpartum Mood Alterations)
- Bowel: fluids and high-fibre foods, bulk laxatives; for hemorrhoids/perineal tenderness: pain meds, doughnut cushion, Sitz baths, ice compresses
- Breast and pelvic exam: watch for Staphylococcal or Streptococcal mastitis/abscess, ± Pap smear at 6 wk

Physiological Changes Postpartum
- uterus weight rapidly diminishes through catabolism, cervix loses its elasticity and regains firmness
  - should involute ~1 cm below umbilicus per day in first 4-5 d, reaches non-pregnant state in 4-6 wk postpartum
- ovulation resumes in ~45 d for non-lactating women and within 3-6 mo for lactating women
- lochia: normal vaginal discharge postpartum, uterine decidual tissue sloughing
  - decreases and changes in colour from red (lochia rubra; presence of erythrocytes, 3-4 d) → pale (lochia serosa) → white / yellow (lochia alba; residual leukorrhea) over 3-6 wk
  - foul-smelling lochia suggests endometritis

Breastfeeding Problems
- inadequate milk: consider domperidone
- breast engorgement: cool compress, manual expression/pumping
- nipple pain: clean milk off nipple after feeds, moisture cream, topical steroid if needed
- mastitis: treat promptly (see Postpartum Pyrexia, OB47)
- inverted nipples: makes feeding difficult
- maternal medications: may require pediatric consultation (see Breastfeeding and Drugs)

Bladder Dysfunction
- pelvic floor prolapse can occur after vaginal delivery
- stress or urge urinary incontinence common
- increased risk with instrumental delivery or prolonged second stage
- conservative management: pelvic floor retraining with Kegel exercises, vaginal cone, or pessaries, lifestyle modifications (e.g. limit fluid, caffeine intake)
- surgical management: minimally invasive procedures (tension-free vaginal tape, transobturator tape, midurethral sling)

Puerperal Pain
- “after pains” common in 1st 3 d due to uterine contractions; encourage simple analgesia
- ice packs can be used on perineum if painful
- encourage regular analgesia and stool softener

Breastfeeding and Drugs

Table 25. Drug Safety During Breastfeeding

<table>
<thead>
<tr>
<th>Safe During Breastfeeding</th>
<th>Contraindicated When Breastfeeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesics (e.g. acetaminophen, NSAIDs)</td>
<td>Chloramphenicol (bone marrow suppression)</td>
</tr>
<tr>
<td>Anticoagulants (e.g. heparin)</td>
<td>Cyclophosphamide (immune system suppression)</td>
</tr>
<tr>
<td>Antidepressants (e.g. sertraline, fluoxetine, TCAs)</td>
<td>Sulphonamides (in G6PD deficiency, can lead to hemolysis)</td>
</tr>
<tr>
<td>Antiepileptics (e.g. phenytoin, carbamazepine, valproic acid)</td>
<td>Nitrofurantoin (in G6PD deficiency, can lead to hemolysis)</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Tetracycline</td>
</tr>
<tr>
<td>Antimicrobials (e.g. penicillins, aminoglycosides, cephalosporins)</td>
<td>Lithium</td>
</tr>
<tr>
<td>β-adrenergics (e.g. propanolol, labetalol)</td>
<td>Cocaine</td>
</tr>
<tr>
<td>Insulin</td>
<td>Phenindione</td>
</tr>
<tr>
<td>Steroids</td>
<td>Bromocriptine</td>
</tr>
<tr>
<td>OCP (low dose) – although may decrease breast milk production</td>
<td>Anti-neoplastics and immunosuppressants</td>
</tr>
<tr>
<td></td>
<td>Psychotropic drugs (relative contraindication)</td>
</tr>
<tr>
<td></td>
<td>redniases/SEX hormones</td>
</tr>
<tr>
<td></td>
<td>Tetracycline/Tretinoin</td>
</tr>
</tbody>
</table>

Breastfeeding: Contraindicated Drugs

BREAST
- Bromocriptine/Benzodiazepines
- Radioactive isotopes/Rizatriptan
- Ergotamine/Ethosuximide
- Amiodarone/Amphetamines
- Stimulant laxatives/Sex hormones
- Tetracycline/Tretinoin
## Table 26. Common Medications

<table>
<thead>
<tr>
<th>Drug Name (Brand Name)</th>
<th>Dosing Schedule</th>
<th>Indications/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>betamethasone valerate (Celestone®)</td>
<td>12 mg IM q24h x 2 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>carboprost (Hemabate®)</td>
<td>0.25 mg IM/MM q15min; max 2 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>cefazolin</td>
<td>2 g IV then 1 g q8h</td>
<td>GBS prophylaxis (penicillin allergic and not at risk for anaphylaxis)</td>
</tr>
<tr>
<td>clindamycin</td>
<td>900 mg IV q8h</td>
<td>Used in endometritis</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>6 mg IM q12h x 4 doses</td>
<td>Enhancement of fetal pulmonary maturity for PTL</td>
</tr>
<tr>
<td>dinoprostone (Cervidil®: PGE2 impregnated thread)</td>
<td>10 mg PV (remove after 12 h) max 3 doses</td>
<td>Induction of labour Advantage: can remove if uterine hyperstimulation</td>
</tr>
<tr>
<td>doxylamine succinate (Diclectin®)</td>
<td>2 tabs qhs + 1 tab qAM + 1 tab qPM max 8 tabs/d</td>
<td>Each tablet contains 10 mg doxylamine succinate with vitamin B6 Used for hyperemesis gravidarum</td>
</tr>
<tr>
<td>erythromycin</td>
<td>500 mg IV q6h</td>
<td>GBS prophylaxis (penicillin allergic and at risk for anaphylaxis)</td>
</tr>
<tr>
<td>folic acid</td>
<td>0.4-1 mg PO OD x 1-3 mo preconception and T1 5 mg PO OD with past Hx of NTD</td>
<td>Prevention of oNTD</td>
</tr>
<tr>
<td>methotrexate</td>
<td>50 mg/m² IM or 50 mg PO x 1 dose</td>
<td>For ectopic pregnancy or medical abortion</td>
</tr>
<tr>
<td>methylergonovine maleate (Ergotamine®)</td>
<td>0.25 mg IM/MM q5min up to 1.25 mg or IV bolus 0.125 mg</td>
<td>Treatment of uterine atony</td>
</tr>
<tr>
<td>misoprostol (Cytotec®)</td>
<td>600-1000 µg P9 x 1 dose 400 µg PO/SL x 1 dose or 800 µg PV x 1 dose, 3-7 d after methotrexate</td>
<td>For treatment of PPH For medical abortion/retained products of conception Also used for NSAID-induced ulcers (warn patients of contraindications)</td>
</tr>
<tr>
<td>oxytocin (Pitocin®)</td>
<td>0.5-2.0 mL/min IV, or 10 U/L NS increase by 1-2 mL/min q20-60min max 36-48 mL/min 10 U IM at delivery of anterior shoulder and of placenta 20 U/L NS or RL IV continuous infusion</td>
<td>Augmentation of labour (also induction of labour) Prevention of uterine atony Treatment of uterine atony</td>
</tr>
<tr>
<td>Penicillin G</td>
<td>5 million U IV then 2.5 million U IV q4h until delivery</td>
<td>GBS prophylaxis</td>
</tr>
<tr>
<td>PGE2 gel (Prostin® gel)</td>
<td>0.5 mg PV q6-12h; max 3 doses</td>
<td>Induction of labour</td>
</tr>
<tr>
<td>Rh IgG (Rhogam®)</td>
<td>300 µg IM x 1 dose</td>
<td>Given to Rh negative women • Routinely at 28 wk GA • Within 72 h of birth of Rh+ fetus • Positive Kleihauer-Betke test • With any invasive procedure in pregnancy • Ectopic pregnancy • Antepartum hemorrhage • Miscarriage or therapeutic abortion (dose: 50 µg IM only)</td>
</tr>
</tbody>
</table>

Common Discharge Medications

- Oxycodone IR 5-10 mg PO q4-6h PRN
- Docusate sodium 100 mg PO bid

Misoprostol (Cytotec®) is also indicated to protect against NSAID-induced gastric ulcers in non-pregnant individuals. The use of misoprostol for cytoprotection is contraindicated in pregnancy; warn female patients of this contraindication.
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<table>
<thead>
<tr>
<th>Acronym</th>
<th>Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>AION</td>
<td>anterior ischemic optic neuropathy</td>
</tr>
<tr>
<td>AMD</td>
<td>age-related macular degeneration</td>
</tr>
<tr>
<td>BCVA</td>
<td>best corrected visual acuity</td>
</tr>
<tr>
<td>BRAO</td>
<td>branch retinal artery occlusion</td>
</tr>
<tr>
<td>BRVO</td>
<td>branch retinal vein occlusion</td>
</tr>
<tr>
<td>C:D</td>
<td>cup to disc ratio</td>
</tr>
<tr>
<td>CMV</td>
<td>cytomegalovirus</td>
</tr>
<tr>
<td>CRAO</td>
<td>central retinal artery occlusion</td>
</tr>
<tr>
<td>D</td>
<td>diopter</td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
</tr>
<tr>
<td>DR</td>
<td>diabetic retinopathy</td>
</tr>
<tr>
<td>EOM</td>
<td>extraocular movement</td>
</tr>
<tr>
<td>FML</td>
<td>fluoromethalone</td>
</tr>
<tr>
<td>GAT</td>
<td>Goldmann applanation tonometry</td>
</tr>
<tr>
<td>GCA</td>
<td>giant cell arteritis</td>
</tr>
<tr>
<td>HRT</td>
<td>Heidelberg retinal tomography</td>
</tr>
<tr>
<td>IDO</td>
<td>intracranial ophthalmoplegia</td>
</tr>
<tr>
<td>IOL</td>
<td>intraocular lens</td>
</tr>
<tr>
<td>IOPT</td>
<td>intraocular pressure</td>
</tr>
<tr>
<td>LASIK</td>
<td>laser-assisted in situ keratomileusis</td>
</tr>
<tr>
<td>INO</td>
<td>internuclear ophthalmoplegia</td>
</tr>
<tr>
<td>MS</td>
<td>multiple sclerosis</td>
</tr>
<tr>
<td>OCT</td>
<td>optical coherence tomography</td>
</tr>
<tr>
<td>OHT</td>
<td>ocular hypertension</td>
</tr>
<tr>
<td>PACG</td>
<td>primary angle-closure glaucoma</td>
</tr>
<tr>
<td>PDR</td>
<td>proliferative diabetic retinopathy</td>
</tr>
<tr>
<td>PDT</td>
<td>photodynamic therapy</td>
</tr>
<tr>
<td>PERRLA</td>
<td>pupils equal, round, and reactive to light and accommodation</td>
</tr>
<tr>
<td>POAG</td>
<td>primary open-angle glaucoma</td>
</tr>
<tr>
<td>PRK</td>
<td>photorefractive keratectomy</td>
</tr>
<tr>
<td>PVD</td>
<td>posterior vitreous detachment</td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
</tr>
<tr>
<td>RAPD</td>
<td>relative afferent pupillary defect</td>
</tr>
<tr>
<td>RO</td>
<td>retinal detachment</td>
</tr>
<tr>
<td>ROP</td>
<td>retinopathy of prematurity</td>
</tr>
<tr>
<td>SLE</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>SPK</td>
<td>superficial punctate keratitis</td>
</tr>
<tr>
<td>TIA</td>
<td>transient ischemic attack</td>
</tr>
<tr>
<td>VEGF</td>
<td>vascular endothelial growth factor</td>
</tr>
<tr>
<td>YAG</td>
<td>yttrium aluminum garnet</td>
</tr>
</tbody>
</table>

## Basic Anatomy Review

### Figure 1. Anatomy of the eye

![Diagram of the eye](https://example.com/diagram.png)

- **Tendon of superior rectus muscle**
- **Ciliary muscle and body**
- **Conjunctival fornix**
- **Lens**
- **Cornea**
- **Palpebral conjunctiva**
- **Bulbar conjunctiva**
- **Meibomian gland**
- **Eyelash**

### Figure 2. Layers of the retina

![Diagram of the retina](https://example.com/diagram.png)

**Retinal Layers (10):**

1. Inner limiting membrane
2. Nerve fibre layer
3. Ganglion cell layer
4. Inner plexiform layer
5. Inner nuclear layer
6. Outer plexiform layer
7. Outer nuclear layer
8. Outer limiting membrane
9. Photoreceptor layer
10. Retinal pigmented epithelium

**CELL TYPES:**

- Amacrine cells
- Bipolar cells
- Horizontal cells
- Ganglion cells
- Rod nuclei
- Cone nuclei
- Rod cells
- Cone cells
- Pigmented cells
- Bruch’s membrane
- choroid

**Light Rays:**

- Vitreous humour
- Optic nerve fibres

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Differential Diagnoses of Common Presentations

Loss of Vision

**Transient (seconds to hours)**
- Transient ischemic attack (TIA)
- Migraine with aura
- Cornea/Anterior Segment
  - Corneal edema
  - Hyphema
  - Acute angle-closure glaucoma
  - Trauma/foreign body

**Acute (seconds to days)**
- Vitreous/Retina/Optic Nerve
  - Vitreous hemorrhage
  - RD
  - Retinal artery/vein occlusion
  - Acute macular lesion
  - Optic neuritis
  - Temporal arteritis
  - Anterior ischemic optic neuropathy (AION)
- Cortical/Other
  - Occipital infarction/hemorrhage
  - Cortical blindness
  - Functional (non-organic, diagnosis of exclusion)

**Chronic (weeks to months)**
- Cornea/Anterior Segment
  - Corneal dystrophy/scarring/edema
  - Refractive error
  - Cataract
  - Glaucoma
- Vitreous/Retina/Optic Nerve
  - AMD
  - DR
  - Retinal vascular insufficiency
  - Compressive optic neuropathy (intracranial mass, orbital mass)
  - Intraocular neoplasm
  - Retinitis pigmentosa
- Cortical/Other
  - Pituitary adenoma
  - Medication-induced (sildenafil, amiodarone)
  - Nutritional deficiency
  - Papilledema

**Top 3 Differential Diagnosis of Acute Loss of Vision**
- Vitreous hemorrhage
- Retinal artery/vein occlusion
- RD

**Top 3 Differential Diagnosis of Chronic Loss of Vision**
- Reversible
  - Cataract
  - Refractive error
  - Corneal dystrophy
- Irreversible
  - AMD
  - Glaucoma
  - DR

Note: Anti-VEGF treatment for exudative AMD and diabetic macular edema may reverse some vision loss.

Figure 3. Tear drainage from the eye (lacrimal apparatus)

Figure 4. Loss of vision
Red Eye
- lids/orbit/lacrimal system
  - hordeolum/chalazion
  - blepharitis
  - entropion/ectropion
  - foreign body/laceration
  - dacryocystitis/dacryoadenitis
- conjunctiva/sclera
  - subconjunctival hemorrhage
  - conjunctivitis
  - dry eyes
  - pterygium
  - episcleritis/scleritis
  - preseptal/orbital cellulitis
- cornea
  - foreign body (including contact lens)
  - keratitis
  - abrasion, laceration
  - ulcer
- anterior chamber
  - anterior uveitis (iritis, iridocyclitis)
  - acute glaucoma
  - hyphema (blood in anterior chamber)
  - hypopyon (pus in anterior chamber)
other
  - trauma
  - post-operative
  - endophthalmitis
  - pharmacologic (e.g. prostaglandin analogs)

Ocular Pain
- differentiate from eye fatigue (asthenopia)
- ocular surface disease
- herpes zoster prodrome
- trauma_foreign body
- blepharitis
- keratitis
- corneal abrasion, corneal ulcer
- acute glaucoma
- acute uveitis
- scleritis (rarely episcleritis)
- optic neuritis

Photophobia (Severe Light Sensitivity)
- corneal abrasion, corneal ulcer
- keratitis
- acute angle-closure glaucoma
- iritis
- meningitis, encephalitis
- migraine
- subarachnoid hemorrhage (SAH)

Diplopia (Double Vision)
- binocular diplopia (occurs with both eyes open, eliminated with occlusion of either eye)
  - strabismus
  - CN palsy (III, IV, VI)
    - ischemia (DM)
    - tumour
    - trauma
  - myasthenia gravis
  - muscle restriction/entrapment
  - thyroid ophthalmopathy
  - INO
    - multiple sclerosis
    - brainstem infarct
- monocular diplopia (occurs with one eye open, remains with occlusion of unaffected eye)
  - refractive error
  - strands of mucus in tear film
  - keratoconus
  - cataracts
  - dislocated lens
  - peripheral laser iridotomy

Ocular Problems in the Contact Lens Wearer
- SPK from dry eyes
- solution hypersensitivity
- tight lens syndrome
- corneal abrasion
- giant papillary conjunctivitis/contact lens allergy
- limbal stem cell deficiency
- corneal neovascularization
- sterile corneal infiltrates (immunologic)
- infected ulcers (Pseudomonas, Acanthamoeba)

Floaters
- PVD (often secondary to age-related vitreous syneresis)
- vitreous hemorrhage
- retinal tear detachment
- intermediate uveitis (pars planitis)
- posterior uveitis (chorioretinitis)

Acute Painless Vision Loss
- vitreous hemorrhage
- retinal artery/vein occlusion
- RD
- AION
- optic neuritis
- amaurosis fugax/TIA/stroke

Flashes of Light (Photopsia)
- PVD (often secondary to age-related vitreous syneresis)
- retinal tear detachment
- migraine with aura
Table 1. Common Differential Diagnoses of Red Eye

<table>
<thead>
<tr>
<th></th>
<th>Conjunctivitis</th>
<th>Acute Iritis</th>
<th>Acute Glaucoma</th>
<th>Keratitis (Corneal Abrasion/Ulcer)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Discharge</strong></td>
<td>Bacterial: purulent</td>
<td>No</td>
<td>No</td>
<td>Profuse tearing</td>
</tr>
<tr>
<td></td>
<td>Viral: serous/mucoid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Allergic: mucous</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td>No</td>
<td>++ (tender globe)</td>
<td>+++ (nausea)</td>
<td>++ (on blinking)</td>
</tr>
<tr>
<td><strong>Photophobia</strong></td>
<td>No</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Blurred Vision</strong></td>
<td>No</td>
<td>+</td>
<td>+++</td>
<td>Varies</td>
</tr>
<tr>
<td><strong>Pupil</strong></td>
<td>Normal</td>
<td>Smaller</td>
<td>Fixed in mid-dilation</td>
<td>Same or smaller</td>
</tr>
<tr>
<td><strong>Injection</strong></td>
<td>Conjunctiva with limbal pallor</td>
<td>Ciliary flush</td>
<td>Diffuse</td>
<td>Diffuse</td>
</tr>
<tr>
<td><strong>Cornea</strong></td>
<td>Normal</td>
<td>Keratic precipitates</td>
<td>Cloudy</td>
<td>Infiltrate, edema, epithelial defects</td>
</tr>
<tr>
<td><strong>IOP</strong></td>
<td>Normal</td>
<td>Varies</td>
<td>Increased markedly</td>
<td>Normal or increased</td>
</tr>
<tr>
<td><strong>Anterior Chamber</strong></td>
<td>Normal</td>
<td>+ + + Cells and flare</td>
<td>Shallow</td>
<td>Cells and flare or normal</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td>Large, tender pre-auricular node(s) if viral</td>
<td>Posterior synechieae</td>
<td>Coloured halos</td>
<td>Nausea and vomiting</td>
</tr>
</tbody>
</table>

Ocular Emergencies

These require urgent consultation to an ophthalmologist for management

**Sight Threatening**
- lid/globe lacerations
- chemical burn
- corneal ulcer
- gonococcal conjunctivitis
- acute iritis
- acute glaucoma
- CRAO
- intraocular foreign body
- RD (especially when macula threatened)
- endophthalmitis
- GCA

**Life Threatening**
- proptosis (rule out cavernous sinus fistula or thrombosis)
- CN III palsy with dilated pupil (intracranial aneurysm or externally compressive neoplastic lesion)
- papilledema (elevated increased intracranial pressure work up)
- orbital cellulitis
- leukocoria: white reflex (absent red reflex, must rule out retinoblastoma)

The Ocular Examination

**Visual Acuity – Distance**
- Snellen Acuity (Figure 5) = smallest line patient can read on the chart
- e.g. 20/40 = what the patient can see at 20 feet (numerator), what a “normal” person can see at 40 feet (denominator)
- distance visual acuity should be tested with distance glasses on in order to obtain best corrected visual acuity
- testing hierarchy for low vision: Snellen acuity (20/x) → counting fingers at a given distance (CF) → hand motion (HM) → light perception with projection (LP with projection) → light perception (LP) → no light perception (NLP)
- legal blindness is BCVA that is ≤20/200 in best eye
- minimum visual requirements to operate a non-commercial automobile in Ontario are: 20/50 BCVA with both eyes open and examined together, 120° continuous horizontal visual field, and 15° continuous visual field above and below fixation

Not every red eye has conjunctivitis
Visual Acuity – Near
- use pocket visual chart (Rosenbaum Pocket Vision Screener)
- record Jaeger (J) or Point number and testing distance (usually 30 cm) e.g. J2 @ 30 cm
- conversion to distance VA possible (e.g. immobile patient, no distance chart available)

Visual Acuity for Infants, Children, Non-English Speakers, and Dysphasics
- newborns
  - VA cannot be tested
- 3 mo-3 yr (can only assess visual function, not acuity)
  - test each eye for fixation symmetry using an interesting object
  - normal function noted as “CSM” = central, steady, and maintained
- 3 yr until alphabet known
  - pictures or letter cards/charts such as HOTV or Sheridan-Gardner test (children point to optotypes on a provided matching card)
  - tumbling “E” chart

Colour Vision
- test with Ishihara pseudoisochromatic plates
- record number of correctly identified plates presented to each eye, specify incorrect plates
- important for testing optic nerve function (e.g. optic neuritis, chloroquine use, thyroid ophthalmopathy)
- note: red-green colour blindness is sex-linked and occurs in 7-10% of males

VISUAL FIELDS
- test “visual fields by confrontation” (4 quadrants, each eye tested separately) for estimation of visual field loss
- accurate, quantifiable assessment with automated visual field testing (Humphrey or Goldmann) or Tangent Screen
- use Amsler grid (each eye tested separately) to check for central or paracentral scotomas (island-like gaps in the vision) in patients with AMD

PUPILS
- use reduced room illumination with patient focusing on distant fixed object to prevent “near reflex”
- examine pupils for shape, size, symmetry, and reactivity to light (both direct and consensual response)
- test for RAPD with swinging flashlight test, check by reverse RAPD if one pupil non-reactive
- test pupillary constriction portion of near reflex by bringing object close to patient’s nose
- “normal” pupil testing often noted as PERRLA (pupils equal, round, and reactive to light and accommodation)

ANTERIOR CHAMBER DEPTH
- shine light tangentially from temporal side
- if >2/3 of nasal side of iris in shadow → shallow anterior chamber

The van Herick Method
- shine thin-angled slit beam onto the peripheral cornea of each eye, view at a 60° angle from the beam
- estimate depth between the posterior surface of the cornea and the iris as a proportion of corneal thickness
- ratios ≤1/4 implies risk of occludable angle; however, if >1/4 this does not rule out. Gonioscopy is gold-standard

Gonioscopy
- allows direct visualization of the angle structures using mirrored contact lens
- angle considered open if trabecular meshwork, scleral spur, and iris processes are visualized
- angle considered narrow (occludable) if only Schwalbe’s line (the termination of Descemet’s membrane) or a small portion of the trabecular meshwork is seen
- angle considered open if scleral spur seen (insertion point of ciliary body muscles)
EXTRAOCULAR MUSCLES

Alignment
- Hirschberg corneal reflex test
  - examine in primary position of gaze (i.e. straight ahead) with patient focusing on distant object
  - shine light into patient's eyes from ~30 cm away
  - corneal light reflex should be symmetric and at the same position on each cornea
- strabismus testing as indicated (cover test, cover-uncover test, prism testing)
  (see Strabismus, OP38)

Movement
- examine movement of eyeball through six cardinal positions of gaze
- ask patient if diplopia or pain is present in any position of gaze
- observe for horizontal, vertical, or rotatory nystagmus (rhythmic, oscillating movements of the eye)
- resolving horizontal nystagmus at end-gaze is usually normal
- see sidebar for cranial nerve innervation of extraocular muscles

Diplopia
- major symptom associated with dysfunction of extraocular muscles or abnormalities of the motor nerves innervating these muscles
- must first determine whether diplopia is monocular or binocular
- determine whether diplopia was sudden onset (due to an acute event such as ischemia) or gradual (due to progressive process such as tumour or inflammation)
- with myasthenia gravis, diplopia and ptosis usually worsen on prolonged upgaze; can rule out with a 'Tensilon' test (see Neurology, N40)
- if suspect compressive lesion (most commonly seen with CN III palsy with a blown pupil), need MRI and angiography to rule out aneurysm or tumour
- new-onset diplopia that disappears with occlusion of either eye (binocular diplopia) needs urgent referral while chronic binocular diplopia and monocular diplopia should be referred non-urgently

Figure 9. Diplopia

EXTERNAL EXAMINATION
- four Ls
  - lymph nodes (preauricular, submandibular)
  - lids
  - lashes
  - lacrimal system
SLIT-LAMP EXAMINATION
- systematically examine all structures of the anterior segment and anterior vitreous (for structures see Figure 1)
- when necessary, use:
  - fluorescein dye: stains Bowman’s membrane in de-epithelialized cornea; dye appears fluorescent green with cobalt blue filtered light
  - Rose Bengal dye: stains devitalized corneal epithelium
- special lenses (78 or 90 D) used with the slit-lamp allow a binocular, stereoscopic, inverted and flipped view of the fundus and vitreous

TONOMETRY
- measurement of IOP
- normal range is 9-21 mmHg (average 15 mmHg)
- IOP has diurnal variation, so always record the time of day at which the measurement was taken
- commonly measured by:
  - Goldmann Applanation Tonometry (GAT): clinical gold standard, performed using the slit-lamp with special tip (prism)
  - Tono-Pen®: benefit is portability and use of disposable probe tips. Use when cornea is scarred/ asymmetric (GAT inaccurate)
  - air puff (non-contact and least reliable)
- use topical anesthetic for GAT and Tono-Pen®; apply fluorescein dye when using GAT

OPHTHALMOSCOPY/FUNDOSCOPY
- performed with
  - direct ophthalmoscope (monocular with small field of view, only posterior pole visualized)
  - slit-lamp with 78 or 90 D lens (binocular view, visualization to mid-periphery of retina)
  - indirect ophthalmoscope with headlamp and 20 or 28 D lens (binocular view, visualization of entire retina to ora serrata/edge of retina)
- best performed with pupils dilated (for list of mydriatics and cycloplegics see Table 11, OP45)
  1. assess red reflex
     - light reflected off the retina produces a “red reflex” when viewed from ~1 foot away
     - anything that interferes with the passage of light will diminish the red reflex (e.g. large vitreous hemorrhage, cataract, retinoblastoma)
  2. examine the posterior segment of the eye
     - vitreous
     - optic disc (colour, C:D ratio, sharpness of disc margin)
     - macula (~1.5-2 disc diameters temporal to disc), fovea (foveal light reflex)
     - retinal vessels
     - retinal background
- contraindications to pupillary dilatation
  - shallow anterior chamber – can precipitate acute angle-closure glaucoma
  - iris-supported anterior chamber lens implant
  - potential neurologic abnormality requiring pupil evaluation
  - use caution with cardiovascular abnormality – mydriatics may cause tachycardia

REFRACTION
- two techniques used
  - flash/streak retinoscopy: refractive error determined objectively by the examiner using lenses and retinoscope
    - manifest: subjective trial using loose lenses or a phoropter (device the patient looks through that is equipped with lenses)
    - a typical lens prescription would contain
      - sphere power in D (measurement of refractive power of lens, equal to reciprocal of focal length in meters)
      - cylinder power in D to correct astigmatism (always positive value)
      - axis of cylinder in degrees
      - “add” (bifocal/progressive reading lens) for presbyopes
      - e.g. -1.50 + 1.00 x 120 degrees, add +2.00

REFRACTIVE EYE SURGERY
- permanently alters corneal refractive properties by ablating tissue to change curvature of the cornea
- used for correction of myopia, hyperopia, and astigmatism
- common types include PRK and LASIK (see Surgical Ophthalmology, OP44)
- potential risks/side-effects: infection, under/overcorrection, decreased night vision (nyctalopia), corneal haze, dry eyes, regression, complete sever of corneal flap (LASIK only)
Table 2. Optics

<table>
<thead>
<tr>
<th>Pathophysiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emmetropia</strong></td>
<td><em>Image of distant objects focus exactly on the retina</em></td>
<td><em>No refractive error</em></td>
<td></td>
</tr>
<tr>
<td><strong>Myopia</strong></td>
<td><em>Globe too long relative to refractive mechanisms, or refractive mechanisms too strong</em></td>
<td><em>“Nearsightedness” – Usually presents in 1st or 2nd decade, stabilizes in 2nd and 3rd decade; rarely begins after age 25 except in patients with DM or cataracts</em></td>
<td><em>Retinal tear/ detachment, macular hole, open angle glaucoma</em></td>
</tr>
<tr>
<td></td>
<td><em>Light rays from distant object focus in front of retina → blurring of (distance) vision</em></td>
<td><em>Blurring of distance vision; near vision usually unaffected</em></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperopia</strong></td>
<td><em>Globe too short relative to refractive mechanisms, or refractive mechanisms too weak</em></td>
<td><em>“Farsightedness” – Youth: usually do not require glasses (still have sufficient accommodative ability to focus image on retina), but may develop accommodative esotropia (see Strabismus, OP38)</em></td>
<td><em>Angle-closure glaucoma, particularly later in life as lens enlarges</em></td>
</tr>
<tr>
<td></td>
<td><em>Light rays from distant object focus behind retina → blurring of near ± distant vision</em></td>
<td><em>30s-40s: blurring of near vision due to decreased accommodation, may need reading glasses</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>May be developmental or due to any etiology that shortens globe</em></td>
<td><em>&gt;50s: blurring of distance vision due to severely decreased accommodation</em></td>
<td></td>
</tr>
<tr>
<td><strong>Astigmatism</strong></td>
<td><em>Light rays not refracted uniformly in all meridians due to non-spherical surface of cornea or non-spherical lens (e.g. football-shaped)</em></td>
<td><em>Affects ~30% of population, with prevalence increasing with age</em></td>
<td><em>Correct with cylindrical lens (if regular), try contact lens (if irregular)</em></td>
</tr>
<tr>
<td></td>
<td><strong>Two types</strong></td>
<td><em>Mild astigmatism unnoticeable</em></td>
<td><em>Refractive eye surgery</em></td>
</tr>
<tr>
<td></td>
<td></td>
<td><em>Higher amounts of astigmatism may cause blurry vision, squinting, asthenopia, or headaches</em></td>
<td></td>
</tr>
<tr>
<td><strong>Presbyopia</strong></td>
<td><em>Normal aging process (&gt;40 yr)</em></td>
<td><em>Correct with positive diopter/ convex/ “plus” lenses to converge light rays</em></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Hardening/reduced deformability of lens results in decreased accommodative ability</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Accommodative power is 14D at age 10, diminishes to 3.5D by age 40 yr</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>Near images cannot be focused onto the retina (focus is behind the retina as in hyperopia)</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anisometropia</strong></td>
<td><em>Difference in refractive errors between eyes</em></td>
<td></td>
<td><em>Second most common cause of amblyopia in children</em></td>
</tr>
</tbody>
</table>

**Imaging Modalities**

- **adaptive optics scanning laser ophthalmology – optical coherence tomography (SLO-OCT)**
  - combines the surface detail of confocal ophthalmoscopy with the internal detail of OCT
  - allows 3D OCT images, volume and area maps, and retinal thickness maps, at the resolution of living rods and cones
  - can visualize photoreceptors, nerve fibers and blood cells in retinal capillaries
- **CT, MRI**
  - orbital imaging, particularly in orbital trauma and neuro-ophthalmology
- **fluorescein angiography**
  - non-invasive evaluation of vascular pattern of the fundus
  - wide-field fluorescent angiogram
  - commonly used in AMD, DR, retinal vascular diseases
- **indocyanine green angiography**
  - uses infra-red light and intravenous ICG dye for imaging of choroidal structure
  - particularly useful to detect polyoidal vasculopathy (variant of AMD) more commonly present among Asian patients
• **HRT**
  ▪ confocal scanning laser tomography of retinal nerve head and surrounding nerve fiber layer
  ▪ used to assess extent of structural glaucomatous changes
• **OCT**
  ▪ non-invasive, cross-sectional, high-resolution imaging of vitreous, retinal layers, optic nerve
  ▪ commonly used to assess macular pathology/edema/holes/cysts, AMD progression, epiretinal membrane, RD
• **anterior segment optical coherence tomography (AS-OCT)**
  ▪ non-invasive, cross-sectional, high-resolution imaging of cornea, aqueous, iris, angle, and lens
• **perimetry**
  ▪ quantitative evaluation of visual fields, used to screen for scotomas and monitor progression (e.g. in glaucoma)
• **ultrasonography**
  ▪ evaluation of orbit in real-time. A-scans (one-dimensional), B-scans (two-dimensional), ultrasound biomicroscopy (UBM) (used for imaging the cornea, iris, angle) and Doppler are all used (e.g. large RDs, foreign bodies, monitoring intraocular tumours)

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### The Orbit

#### Globe Displacement

<table>
<thead>
<tr>
<th>Table 3. Exophthalmos (Proptosis) and Enophthalmos</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exophthalmos (Proptosis)</strong></td>
</tr>
<tr>
<td><strong>Definition</strong></td>
</tr>
<tr>
<td>• Anterior displacement (protrusion) of the globe</td>
</tr>
<tr>
<td>• Exophthalmos generally refers to an endocrine etiology or protrusion of &gt;18 mm (as measured by a Hertel exophthalmometer)</td>
</tr>
<tr>
<td>• Proptosis generally refers to other etiologies (e.g. cellulitis) or protrusion of &lt;18 mm</td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
</tr>
<tr>
<td>• Note: rule out pseudoexophthalmos (e.g. lid retraction)</td>
</tr>
<tr>
<td>• Graves’ disease (unilateral or bilateral, most common cause in adults)</td>
</tr>
<tr>
<td>• Orbital cellulitis (unilateral, most common cause in children)</td>
</tr>
<tr>
<td>• 1° or 2° orbital tumours</td>
</tr>
<tr>
<td>• Orbital/retrobulbar hemorrhage</td>
</tr>
<tr>
<td>• Cavernous sinus thrombosis or fistula</td>
</tr>
</tbody>
</table>

---

### Preseptal Cellulitis

• infection of soft tissue anterior to orbital septum

#### Etiology

• usually follows periorbital trauma or dermal infection

#### Clinical Features

<table>
<thead>
<tr>
<th>Table 4. Clinical Features of Preseptal and Orbital Cellulitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Finding</strong></td>
</tr>
<tr>
<td>Fever</td>
</tr>
<tr>
<td>Lid edema</td>
</tr>
<tr>
<td>Conjunctival injection</td>
</tr>
<tr>
<td>Chemosis</td>
</tr>
<tr>
<td>Proptosis</td>
</tr>
<tr>
<td>Pain on eye movement</td>
</tr>
<tr>
<td>Ocular mobility</td>
</tr>
<tr>
<td>Vision</td>
</tr>
<tr>
<td>RAPD</td>
</tr>
<tr>
<td>Leukocytosis</td>
</tr>
<tr>
<td>ESR</td>
</tr>
<tr>
<td>Additional findings</td>
</tr>
</tbody>
</table>
Treatment
• systemic antibiotics (suspect *H. influenzae* in children; *S. aureus* or *Streptococcus* in adults)
  • e.g. amoxicillin-clavulanic acid
• if severe or child <1 yr, treat as orbital cellulitis

Orbital Cellulitis
• OCULAR and MEDICAL EMERGENCY
• inflammation of orbital contents posterior to orbital septum
• common in children, elderly, and immunocompromised

Etiology
• usually secondary to sinus/facial/tooth infections or trauma, can also arise from preseptal cellulitis

Clinical Features (see Table 4)

Treatment
• admit, blood cultures x2, orbital CT, IV antibiotics (ceftriaxone + vancomycin) for 1 wk
• surgical drainage of abscess with close follow-up, especially in children

Complications
• optic nerve inflammation, cavernous sinus thrombosis, meningitis, and brain abscess with possible loss of vision, death

Lacrimal Apparatus
• tear film made up of three layers
  • outer oily layer (reduces evaporation): secreted by the Meibomian glands
  • middle watery layer (forms the bulk of the tear film): constant secretion from conjunctival glands and reflex secretion by lacrimal gland with ocular irritation or emotion
  • inner mucinous layer (aids with tear adherence to cornea): secreted by conjunctival goblet cells

• tears drain from the eyes through the upper and lower lacrimal puncta → superior and inferior canaliculi → lacrimal sac → nasolacrimal duct → nasal cavity behind inferior concha (Figure 3)

Dry Eye Syndrome (Keratoconjunctivitis Sicca)

Etiology
• aqueous-deficient (lacrimal pathology)
  • Sjögren syndrome (autoimmune etiology e.g. RA, SLE)
  • non-Sjögren syndrome (idiopathic age-related disease; lacrimal gland scarring e.g. trachoma; decreased secretion e.g. contact lenses, CN VII palsy, anticholinergics, antihistamines, diuretics, β-blockers)
• evaporative (normal lacrimal function, excessive evaporation of aqueous layer)
  • Meibomian gland dysfunction (posterior blepharitis)
  • vitamin A deficiency (xerophthalmia with goblet cell dysgenesis)
  • eyelid abnormalities e.g. ectropion, CN VII palsy (decreased blinking)
  • preserved topical ocular medications
  • contact lenses, allergic conjunctivitis
  • overlap of mixed etiologies is common

Clinical Features
• dry eyes, red eyes, foreign body sensation, blurred vision, tearing
• slit-lamp exam: decreased tear meniscus, decreased tear break-up time (normally should be 10 s), punctate staining of cornea with fluorescein

Investigations
• surface damage observed with fluorescein/Rose Bengal staining
• decreased distance in Schirmer’s test

Complications
• erosions and scarring of cornea

Treatment
• medical: preservative-free artificial tears up to q1h and ointment at bedtime (preservative toxicity becomes significant if used >q1h PRN)
  • for severe cases, cyclosporine ophthalmic emulsion 0.05% (Restasis®) can be used
• procedural: punctal occlusion (punctal plug insertion), lid taping, tarsorrhaphy (sew lids together) if severe
• treat underlying cause
Epiphora (Excessive Tearing)

Etiology
- emotion, pain
- environmental stressor (cold, wind, pollen, sleep deprivation)
- lid/lash malposition: ectropion, entropion, trichiasis
- inflammatory: conjunctivitis, dacryoadenitis, uveitis, keratitis, corneal foreign body
- dry eyes (reflex tearing)
- lacrimal drainage obstruction (congenital failure of canalization, aging, rhinitis, dacryocystitis)
- paradoxical gustatory lacrimation reflex (crocodile tears)

Investigations
- using fluorescein dye, examine for punctal reflux by pressing on canaliculi
- Jones dye test: fluorescein placed in conjunctival cul-de-sac, and cotton applicator placed in nose to detect flow (i.e. rule out lacrimal drainage obstruction)

Treatment
- lid repair for ectropion or entropion
- eyelash removal for trichiasis
- punctal irrigation
- nasolacrimal duct probing (infants)
- tube placement: temporary (Crawford) or permanent (Jones)
- surgical: dacryocystorhinostomy (see Surgical Ophthalmology, OP44) – forming a new connection between the lacrimal sac and the nasal cavity

Dacryocystitis
- acute or chronic infection of the lacrimal sac
- most commonly due to obstruction of the nasolacrimal duct
- commonly associated with S. aureus, S. pneumoniae, Pseudomonas species

Clinical Features
- pain, swelling, redness over lacrimal sac at medial canthus
- epiphora, crusting, ± fever
- digital pressure on the lacrimal sac may extrude pus through the punctum
- in the chronic form, epiphora may be the only symptom

Treatment
- warm compresses, nasal decongestants, systemic and topical antibiotics
- if chronic, obtain cultures by aspiration
- once infection resolves, consider dacryocystorhinostomy (see Surgical Ophthalmology, OP44)

Dacryoadenitis
- inflammation of the lacrimal gland (outer third of upper eyelid)
- acute causes: S. aureus, mumps, EBV, herpes zoster, N. gonorrhoeae
- chronic causes (often bilateral): lymphoma, leukemia, sarcoidosis, tuberculosis, thyroid ophthalmopathy

Clinical Features
- pain, swelling, tearing, discharge, redness of the outer region of the upper eyelid
- chronic form is more common and may present as painless enlargement of the lacrimal gland

Treatment
- supportive: warm compresses, oral NSAIDs
- systemic antibiotics if bacterial cause
- if chronic, treat underlying disorder

Lids and Lashes

Lid Swelling

Etiology
- commonly due to allergy, with shriveling of skin between episodes
- dependent edema on awakening (e.g. CHF, renal or hepatic failure)
- orbital venous congestion due to mass or cavernous sinus fistula
- dermatochalasis (loose skin due to aging or heredity)
- lid cellulitis, thyroid disease (e.g. myxedema), trauma, chemois
Ptosis

- drooping of upper eyelid

Etiology
- aponeurotic: disinsertion or dehiscence of levator aponeurosis (most common)
  - associated with advancing age, trauma, surgery, pregnancy, chronic lid swelling
- mechanical
  - incomplete opening of eyelid due to mass or scarring
- neuromuscular
  - myasthenia gravis (neuromuscular palsy), myotonic dystrophy
  - CN III palsy
  - Horner's syndrome (see Constricted Pupil, Horner's Syndrome, OP32)
- congenital
- pseudoptosis (e.g. dermatochalasis, enophthalmos, contralateral exophthalmos)
- drugs (e.g. high dose opioids, heroin abuse, pregabalin)

Treatment
- surgery (e.g. blepharoplasty, levator resection, Müller’s muscle resection, frontalis sling)

Trichiasis

- eyelashes turned inwards
- may result from chronic inflammatory lid diseases (e.g. blepharitis), Stevens-Johnson syndrome, trauma, burns
- patient complains of red eye, foreign body sensation, significant discomfort, tearing
- may result in corneal ulceration and scarring

Treatment
- topical lubrication, eyelash plucking, electrolysis, cryotherapy

Entropion

- lid margin turns inwards towards globe causing tearing, foreign body sensation, and red eye
- most commonly affects lower lid
- may cause corneal abrasions with secondary corneal scarring

Etiology
- involutional (aging)
- cicatricial (herpes zoster, surgery, trauma, burns)
- orbicularis oculi muscle spasm
- congenital

Treatment
- lubricants, evert lid with tape, surgery

Testing for Entropion
Forced lid closure: Ask patient to tighten lid then open. In entropion, lid rolls inwards

Ectropion

- lid margin turns outward from globe causing tearing and possibly exposure keratitis

Etiology
- involutional (aging)
- paralytic (CN VII palsy)
- cicatricial (burns, trauma, surgery)
- mechanical (lid edema, tumour, herniated fat)
- congenital

Treatment
- topical lubrication, surgery

Testing for Ectropion
Snapback test: Pull eyelid inferiorly. In ectropion, lid remains away from globe

Hordeolum (Stye)

- acute inflammation of eyelid gland: either Meibomian glands (internal lid), glands of Zeis (modified sweat gland) or Moll (modified sebaceous gland in external lid)
- infectious agent is usually S. aureus
- painful, red swelling of lid

Treatment
- warm compresses, lid care, gentle massage
- topical antibiotics (e.g. erythromycin ointment bid)
- usually resolves in 2-5 d
Chalazion
- chronic granulomatous inflammation of Meibomian gland often preceded by an internal hordeolum
- acute inflammatory signs are usually absent
- differential diagnosis: basal cell carcinoma, sebaceous cell adenoma, Meibomian gland carcinoma

Treatment
- warm compresses
- if no improvement after 1 mo, consider incision and curettage
- chronic recurrent lesion must be biopsied to rule out malignancy

Blepharitis
- inflammation of lid margins

Etiology
- two main types
  - staphylococcal (S. aureus): ulcerative, dry scales
  - seborrheic: no ulcers, greasy scales

Clinical Features
- itching, tearing, foreign body sensation
- thickened, red lid margins, crusting, discharge with pressure on lids (“toothpaste sign”)

Complications
- recurrent chalazia
- conjunctivitis
- keratitis (from poor tear film)
- corneal ulceration and neovascularization

Treatment
- warm compresses and lid scrubs with diluted “baby shampoo”
- topical or systemic antibiotics as needed
- if severe, ophthalmologist may prescribe a short course of topical corticosteroids, omega 3 fatty acids

Xanthelasma
- eyelid xanthoma (lipid deposits in dermis of lids)
- appear as pale, slightly elevated yellowish plaques or streaks
- most commonly on the medial upper lids, often bilateral
- associated with hyperlipidemia (~50% of patients)
- common in the elderly, more concerning in the young

Treatment
- excision for cosmesis only, commonly recurs

Conjunctiva
- thin, vascular mucous membrane/epithelium
- bulbar conjunctiva: lines sclera to limbus (junction between cornea and sclera)
- palpebral (tarsal) conjunctiva: lines inner surface of eyelid

Pinguecula
- yellow-white subepithelial deposit of hyaline and elastic tissue adjacent to the nasal or temporal limbus, sparing the cornea
- associated with sun and wind exposure, aging
- common, benign, sometimes enlarges slowly
- may be irritating due to abnormal tear film formation over the deposits
- surgery for cosmesis only
- irritative symptoms may be treated with lubricating drops
**Pterygium**

- fibrovascular, triangular, wing-like encroachment of epithelial tissue onto the cornea, usually nasally
- may induce astigmatism, decrease vision
- excision for chronic inflammation, threat to visual axis, cosmesis
- irritative symptoms may be treated with lubricating drops
- one-third recur after excision, lower recurrence with conjunctival autograft (5%)

**Subconjunctival Hemorrhage**

- blood beneath the conjunctiva, otherwise asymptomatic
- idiopathic or associated with trauma, Valsalva maneuver, bleeding disorders, HTN, anticoagulation
- give reassurance if no other ocular findings, resolves spontaneously in 2-3 wk
- if recurrent, consider medical/hematologic workup

**Conjunctivitis**

**Etiology**

- infectious
  - bacterial, viral, chlamydial, gonococcal, fungal, parasitic
- non-infectious
  - allergic: atopic, seasonal, giant papillary conjunctivitis (contact lens wearers)
  - toxic: irritants, dust, smoke, irradiation
  - secondary to another disorder: dacryocystitis, dacryoadenitis, cellulitis, systemic inflammatory disease

**Clinical Features**

- red eye (conjunctival injection often with limbal pallor), chemosis, subepithelial infiltrates
- itching, foreign body sensation, tearing, discharge, crusting of lashes in the morning, lid edema
- preauricular and/or submandibular nodes
- follicles: pale lymphoid elevations of the conjunctiva, overlain by vessels
- papillae: fibrovascular elevations of the conjunctiva with central network of finely branching vessels (cobblestone appearance)

**ALLERGIC CONJUNCTIVITIS**

**Atopic**

- associated with rhinitis, asthma, dermatitis, hay fever
- small papillae, chemosis, thickened and erythematous lids, corneal neovascularization
- seasonal (pollen, grasses, plant allergens)
- treatment: cool compresses, antihistamine, mast cell stabilizer (e.g. ketotifen, olopatadine), topical corticosteroids

**Giant Papillary Conjunctivitis**

- immune reaction to mucus debris on lenses in contact lens wearers
- large papillae form on superior palpebral conjunctiva
- treatment: clean, change or discontinue use of contact lens

**Vernal Conjunctivitis**

- large papillae (cobblestones) form on superior palpebral conjunctiva with corneal ulcers and keratitis
- seasonal (warm weather)
- occurs in children, lasts for 5-10 yr then resolves
- treatment: consider topical steroid, topical cyclosporine (by ophthalmologist)

**VIRAL CONJUNCTIVITIS**

- serous discharge, lid edema, follicles
- subepithelial corneal infiltrates
- may be associated with rhinorrhea
- preauricular node often palpable and tender
- initially unilateral, often progresses to the other eye
- mainly due to adenovirus – highly contagious for up to 12 d

**Treatment**

- cool compresses, topical lubrication
- usually self-limiting (7-12 d)
- proper hygiene is very important

**Antibiotics vs. Placebo for Acute Bacterial Conjunctivitis**

*Cochrane DB Syst Rev 2012;9:CD001211*

**Purpose:** To assess the benefits and harms of antibiotic therapy in the management of acute bacterial conjunctivitis.

**Criteria:** RCTs with any form of antibiotic treatment compared with placebo including topical, systemic or combined (e.g. antibiotics and steroids) antibiotic treatments.

**Results:** 11 RCTs, 3,673 participants. Topical antibiotics improve early (2-5 d) clinical and microbiological remission rates (RR 1.36, 95% CI 1.15-1.61; RR 1.55; 95% CI 1.37-1.76) and benefit clinical remission and microbiological cure rates at a late time point (6-10 d) (RR 1.21, 95% CI 1.10-1.32; RR 1.37, 95% CI 1.24-1.52). By 6-10 d 41% of cases had resolved in the placebo group. No serious outcomes were reported in any group.

**Conclusion:** The use of antibiotic eye drops is associated with modestly improved rates of clinical and microbiological remission in comparison to placebo. Antibiotic eye drops should therefore be considered in order to speed the resolution of symptoms and infection although acute bacterial conjunctivitis is frequently self-limiting.
BACTERIAL CONJUNCTIVITIS
• purulent discharge, lid swelling, papillae, conjunctival injection, chemosis
• common agents include *S. aureus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*
• in neonates or if sexually active must consider *N. gonorrhoeae* (invades cornea to cause keratitis)
• *C. trachomatis* is the most common cause in neonates

Treatment
• topical broad-spectrum antibiotic
• systemic antibiotics if indicated, especially in neonates and children
• usually a self-limited course of 10-14 d if no treatment, 1-3 d with treatment

GONOCOCCAL AND CHLAMYDIAL CONJUNCTIVITIS
• caused by *N. gonorrhoea* and *C. trachomatis*, respectively
• affects sexually active individuals, neonates (ophthalmia neonatorum) in first 5 days of life when caused by gonorrhea (shorter incubation period) and days 3-14 of life when caused by chlamydia (longer incubation period)
• newborn prophylaxis with 0.5% erythromycin ointment no longer recommended
• causes trachoma and inclusion conjunctivitis (different serotypes)

Trachoma
• leading infectious cause of blindness in the world
• severe keratoconjunctivitis leads to corneal abrasion, ulceration, and scarring
• initially, follicles on superior palpebral conjunctiva
• treatment: topical and systemic tetracycline

Inclusion Conjunctivitis
• chronic conjunctivitis with follicles and subepithelial infiltrates
• most common cause of conjunctivitis in newborns
• newborn prophylaxis with 0.5% erythromycin ointment no longer recommended
• treatment: topical and systemic tetracycline, doxycycline, or erythromycin

Preventing Ophthalmia Neonatorum
*Paediatr Child Health* 2015;20(2):93-96
The use of silver nitrate as prophylaxis for neonatal ophthalmia was instituted in the late 1800s to prevent the devastating effects of neonatal ocular infection with *Neisseria gonorrhoeae*. At that time – during the preantibiotic era – many countries made such prophylaxis mandatory by law. Today, neonatal gonococcal ophthalmia is rare in Canada, but ocular prophylaxis for this condition remains mandatory in some provinces/territories. Silver nitrate drops are no longer available and erythromycin, the only ophthalmic antibiotic eye ointment currently available for use in newborns, is of questionable efficacy. Ocular prophylaxis is not effective in preventing chlamydial conjunctivitis. Applying medication to the eyes of newborns may result in mild eye irritation and has been perceived by some parents as interfering with mother-infant bonding. Physicians caring for newborns should advocate for rescinding mandatory ocular prophylaxis laws. More effective means of preventing ophthalmia neonatorum include screening all pregnant women for gonorrhea and chlamydia infection, and treatment and follow-up of those found to be infected. Mothers who were not screened should be tested at delivery. Infants of mothers with untreated gonococcal infection at delivery should receive ceftriaxone. Infants exposed to chlamydia at delivery should be followed closely for signs of infection.

Sclera
• white fibrous outer protective coat of the eye, composed of irregularly distributed collagen bundles
• continuous with the cornea anteriorly and the dura of the optic nerve posteriorly
• episclera is a thin layer of vascularized tissue between the sclera and conjunctiva

Episcleritis
• immunologically mediated inflammation of episclera
• 1/3 bilateral; simple (80%) or nodular (20%)
• more frequent in women than men (3:1)

Etiology
• mostly idiopathic
• in 1/3 of cases, associated with collagen vascular diseases, infections (herpes zoster, herpes simplex, syphilis), inflammatory bowel disease, rosacea, atopy

Clinical Features
• usually asymptomatic; may have discomfort, heat sensation, red eye (often interpalpebral), rarely pain
• sectoral or diffuse injection of radially-directed vessels, chemosis, small mobile nodules
• blanches with topical phenylephrine (constricts superficial conjunctival vessels)

Treatment
• generally self-limited, recurrent in 2/3 of cases
• topical steroid for 3-5 d if painful (prescribed and monitored by ophthalmologist)
• oral NSAID

Scleritis
• usually bilateral; diffuse, nodular, or necrotizing
• anterior scleritis: pain radiating to face, may cause scleral thinning, in some cases necrotizing
• posterior scleritis: rapidly progressive blindness, may cause exudative RD
  • more common in women and elderly

Etiology
• may be a manifestation of systemic disease
• collagen vascular disease, e.g. SLE, RA, ankylosing spondylitis
• granulomatous, e.g. tuberculosis, sarcoidosis, syphilis
• metabolic, e.g. gout, thyrotoxicosis
• infectious, e.g. S. aureus, S. pneumoniae, P. aeruginosa, herpes zoster
• chemical or physical agents, e.g. thermal, alkali, or acid burns
• idiopathic

Clinical Features
• severe pain, photophobia, red eye, decreased vision
• pain is best indicator of disease progression
• in inflammation of scleral, episcleral, and conjunctival vessels
• may have anterior chamber cells and flare, corneal infiltrate, scleral thinning, scleral edema
• sclera may have a blue hue (best seen in natural light), due to rearranged scleral fibres
• failure to blanch with topical phenylephrine

Treatment
• systemic NSAID or steroid (topical steroids are not effective)
• treat underlying etiology

Cornea

• function
  ▪ transmission of light
  ▪ refraction of light (2/3 of total refractive power of eye)
  ▪ barrier against infection, foreign bodies
• transparency due to avascularity, uniform collagen structure and deturgescence (relative dehydration)
• 6 layers (anterior to posterior): epithelium, Bowman’s membrane, stroma, Dua’s layer, Descemet’s membrane, endothelium (dehydrates the cornea; dysfunction leads to corneal edema)
• extensive sensory fibre network (V1 distribution); therefore abrasions and inflammation (keratitis) are very painful

Foreign Body
• foreign material in or on cornea
• may have associated rust ring if metallic
• patients may note tearing, photophobia, foreign body sensation, red eye
• signs include foreign body, conjunctival injection, epithelial defect that stains with fluorescein, corneal edema, anterior chamber cells/flare

Complications
• abrasion, infection, ulcerating, rust ring, secondary iritis

Treatment
• remove under magnification using local anesthetic and sterile needle or refer to ophthalmology (depending on depth and location)
• treat as per corneal abrasion

Corneal Abrasion
• epithelial defect usually due to trauma (e.g. fingernails, paper, twigs), contact lens (Figure 14)

Clinical Features (Table 5)
• pain, redness, tearing, photophobia, foreign body sensation
• de-epithelialized area stains with fluorescein dye
• pain relieved with topical anesthetic

Complications
• infection, ulceration, recurrent erosion, secondary iritis

Treatment
• topical antibiotic (drops or ointment)
• consider topical NSAID (caution due to risk of corneal melt with prolonged use), cycloplegic (relieves pain and photophobia by paralyzing ciliary muscle), patch
• most abrasions clear spontaneously within 24-48 h
Recurrent Erosions

- recurrent episodes of pain, photophobia, foreign body sensation with a spontaneous corneal epithelial defect
- usually occurs upon awakening
- associated with improper adherence of epithelial cells to the underlying basement membrane

Etiology

- previous traumatic corneal abrasion
- corneal dystrophy
- idiopathic

Treatment

- as for corneal abrasion until re-epithelialization occurs
- topical hypertonic saline ointment at bedtime for 3 mo, topical lubrication
- bandage contact lens, anterior stromal puncture or phototherapeutic keratectomy for chronic recurrences

Corneal Ulcer

Etiology

- local necrosis of corneal tissue due to infection
- infection is usually bacterial, rarely viral, fungal, or protozoan (Acanthamoeba)
- secondary to corneal exposure, abrasion, foreign body, contact lens use (50% of ulcers)
- also associated with conjunctivitis, blepharitis, keratitis, vitamin A deficiency

Clinical Features

- pain, photophobia, tearing, foreign body sensation, decreased VA (if central ulcer)
- corneal opacity that necroses and forms an excavated ulcer with infiltrative base
- overlying corneal epithelial defect that stains with fluorescein
- may develop corneal edema, conjunctival injection, anterior chamber cells/flare, hypopyon, corneal hypoesthesia (in viral keratitis)
- bacterial ulcers may have purulent discharge, viral ulcers may have watery discharge

Complications

- decreased vision, corneal perforation, iritis, endophthalmitis

Investigations

- Seidel test: fluorescein drop on the cornea under cobalt blue filter is used to detect leaking penetrating lesions; any aqueous leaking will dilute the green stain at site of wound

Treatment

- urgent referral to ophthalmology
- culture prior to treatment
- topical antibiotics every hour
- must treat vigorously to avoid complications

Table 5. Corneal Abrasion vs. Corneal Ulcer

<table>
<thead>
<tr>
<th></th>
<th>Abrasion</th>
<th>Ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time Course</td>
<td>Acute (instantaneous)</td>
<td>Subacute (days)</td>
</tr>
<tr>
<td>History of Trauma</td>
<td>Yes</td>
<td>Not usually</td>
</tr>
<tr>
<td>Cornea</td>
<td>Clear</td>
<td>White, necrotic area</td>
</tr>
<tr>
<td>Iris Detail</td>
<td>Clear</td>
<td>Obscured</td>
</tr>
<tr>
<td>Corneal Thickness</td>
<td>Normal</td>
<td>May have crater defect/thinning</td>
</tr>
<tr>
<td>Extent of Lesion</td>
<td>Limited to epithelium</td>
<td>Extension into stroma</td>
</tr>
</tbody>
</table>

Herpes Simplex Keratitis

- usually HSV type 1 (90% of population are carriers)
- may be triggered by stress, fever, sun exposure, immunosuppression

Clinical Features

- pain, tearing, foreign body sensation, red eye, may have decreased vision, eyelid edema
- corneal hypoesthesia
- dendritic (thin and branching) lesion in epithelium that stains with fluorescein

Antiviral Treatment and Other Therapeutic Interventions for Herpes Simplex Virus Epithelial Keratitis

Cochrane DB Syst Rev 2010:12:CD002899

Rates of corneal re-epithelialization after acute HSV corneal epithelial keratitis are similar after treatment with trifluoridine or acyclovir, and significantly better than after treatment with idoxuridine or vidarabine. Brivudine and ganciclovir are not inferior to acyclovir. Combining an antiviral agent with Interferon or corneal epithelial debridement did not improve outcomes overall, but did hasten corneal healing. Debridement with concomitant antiviral treatment was more effective than debridement alone.

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Complications
• corneal scarring (can lead to loss of vision)
• chronic interstitial keratitis due to penetration of virus into stroma
• secondary iritis, secondary glaucoma

Treatment
• topical antiviral such as trifluridine, consider systemic antiviral such as acyclovir
• dendritic debridement
• NO STEROIDS initially – may exacerbate condition
• ophthalmologist must exercise caution if adding topical steroids for chronic keratitis or iritis

Herpes Zoster
• dermatitis of the forehead (CN V1 territory) may involve globe
• Hutchinson's sign: if tip of nose is involved (nasociliary branch of V1) then eye will be involved in ~75% of cases
• if no nasal involvement, eye is involved in 1/3 of patients

Clinical Features
• pain, tearing, photophobia, red eye
• corneal edema, pseudodendrite, SPK
• corneal hypoesthesia

Complications
• corneal keratitis, ulceration, perforation and scarring
• secondary iritis, secondary glaucoma, cataract
• muscle palsies (rare) due to CNS involvement
• occasionally severe post-herpetic neuralgia

Treatment
• oral antiviral (acyclovir, valcyclovir, or famciclovir) immediately
• topical steroids, cycloplegia as indicated for keratitis, iritis
• erythromycin ointment if conjunctival involvement

Keratoconus
• bilateral paracentral thinning and bulging (ectasia) of the cornea to form a conical shape
• usually sporadic, but associated with Down's syndrome, atopy, contact lens use (theorized to be related to chronic vigorous eye rubbing)
• associated with breaks in Descemet's and Bowman's membrane
• results in irregular astigmatism, scarring, stromal edema

Treatment
• attempt correction with spectacles or contact lens
• cross-linking treatment may halt or slow disease progression
• intrastromal corneal ring segments can help flatten the corneal cone
• penetrating keratoplasty (corneal transplant) 90% successful
• post-transplant complications: endophthalmitis, graft rejection, graft failure, graft dehiscence

Arcus Senilis
• hazy white ring in peripheral cornea, <2 mm wide, clearly separated from limbus
• common, bilateral, benign corneal degeneration due to lipid deposition, part of the aging process
• may be associated with hypercholesterolemia if age <40 yr, check lipid profile
• no associated visual symptoms, no complications, no treatment necessary

Kayser-Fleischer Ring
• brown-yellow-green pigmented ring in peripheral cornea, starting inferiorly
• due to deposition of copper pigment in Descemet's membrane
• associated with Wilson's disease
• no associated symptoms or complications of ring
• treat underlying disease
## The Uveal Tract

- Uveal tract (from anterior to posterior) = iris, ciliary body, choroid
- Vascularized, pigmented middle layer of the eye, between the sclera and the retina

## Uveitis

- Uveal inflammation which may involve one, two, or all three parts of the tract
- Idiopathic or associated with autoimmune, infectious, granulomatous, malignant causes
- Should be managed by an optometrist or ophthalmologist
- Anatomically classified as anterior uveitis, intermediate uveitis, posterior uveitis, or panuveitis based on primary site of inflammation

### Table 6. Anatomic Classification of Uveitis

<table>
<thead>
<tr>
<th>Location</th>
<th>Etiology</th>
<th>Clinical Features</th>
<th>Complications</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Irritis  | Usually idiopathic  
|  | Connective tissue diseases  
|  | HLA-B27: reactive arthritis, ankylosing spondylitis, psoriatic arthritis, inflammatory bowel disease  
|  | Non-HLA-B27: juvenile idiopathic arthritis  
|  | Infectious: syphilis, Lyme disease, toxoplasmosis, TB, HSV, herpes zoster  
|  | Other: sarcoidosis, trauma, large abrasion, post ocular surgery  
|  | Inflammation of iris, usually accompanied by cyclitis (inflammation of ciliary body), both = iridocyclitis  
|  | Usually unilateral  
|  | Usually idiopathic  
|  | Mostly idiopathic, secondary causes include sarcoidosis, Lyme disease, and multiple sclerosis  
|  | Bacterial: syphilis, tuberculosis  
|  | Viral: herpes simplex virus, CMV in AIDS  
|  | Fungal: histoplasmosis, candidiasis  
|  | Parasitic: toxoplasmosis (most common cause), toxocara  
|  | Immunosuppression may predispose to any of the above infections  
|  | Autoimmune: Behçet’s disease (triad of oral ulcers, genital ulcers, and posterior uveitis)  
|  | Malignancies (masquerade syndrome): metastatic lesions, malignant melanoma  
|  | Photophobia (due to reactive spasm of inflamed iris muscle), ocular pain, tenderness of the globe, brow ache (ciliary muscle spasm), decreased VA in severe cases with hypopyon), lacrimation  
|  | Ciliary flush (perilimbal conjunctival injection), miosis (spasm of sphincter muscle)  
|  | Anterior chamber “cells” (WBC in anterior chamber due to anterior segment inflammation) and “flare” (protein precipitates in anterior chamber secondary to inflammation), hypopyon (collection of neutrophilic exudates inferiorly in the anterior chamber)  
|  | Occasionally keratic precipitates (clumps of cells on corneal endothelium)  
|  | Iritis typically reduces IOP because ciliary body inflammation causes decreased aqueous production; however, severe iritis, or iritis from herpes simplex and zoster may cause an inflammatory glaucoma (trabeculitis)  
|  | Insidious onset of blurred vision, accompanied by vitreous floaters  
|  | Initial symptoms are usually unilateral but inflammatory changes are usually bilateral and asymmetric  
|  | Associated with anterior uveitis, most severe cases of secondary intermediate uveitis  
|  | Vitreous cells, condensations, and snowballs (vitreous aggregates of inflammatory cells)  
|  | Posterior segment ‘snowbank’ = grey-white fibrovascular plaque at the pars plana  
|  | Painless as choroid has no sensory innervation  
|  | Often no conjunctival or scleral injection present  
|  | Decreased VA  
|  | Floaters (debris and inflammatory cells)  
|  | Vitreous cells and opacities  
|  | Hypopyon formation  
|  | Systemic or sub-tenon/intravitreal steroids and immunosuppressive agents  
|  | Vitrectomy, cryotherapy, or laser photocoagulation to the “snowbank”  
|  | Systemic, topical, or sub-tenon  
|  | Systemic analgesia  
|  | If recurrent episodes, extensive medical workup may be indicated to rule out secondary causes  
|  | Steroids: sub-tenon, intravitreal, or systemic if indicated (e.g. threat of vision loss)
**Lens**

- consists of an outer capsule surrounding a soft cortex and a firm inner nucleus

**Cataracts**

- any opacity of the lens, regardless of etiology
- most common cause of reversible blindness worldwide
- types: nuclear sclerosis, cortical, posterior subcapsular

**Etiology**
- acquired
  - age-related (over 90% of all cataracts)
  - cataract associated with systemic disease (may have juvenile onset)
    - DM
    - metabolic disorders (e.g. Wilson’s disease, galactosemia, homocystinuria)
    - hypocalcemia
  - traumatic (may be rosette shaped)
  - intraocular inflammation (e.g. uveitis)
  - toxic (steroids, phenothiazines)
  - radiation
- congenital
  - high myopia
  - present with altered red reflex or leukocoria
  - treat promptly to prevent amblyopia

**Clinical Features**
- gradual, painless, progressive decrease in VA
- glare, dimness, halos around lights at night, monocular diplopia
- “second sight” phenomenon: patient is more myopic than previously noted, due to increased refractive power of the lens (in nuclear sclerosis only)
  - patient may read without previously needed reading glasses
- diagnosis by slit-lamp exam, and by noting changes in red reflex using ophthalmoscope
- may impair view of retina during fundoscopy

**Treatment**
- medical: attempt correction of refractive error, no strong evidence suggesting benefit of vitamin supplementation
- surgical: definitive treatment
  - indications for surgery
    - to improve visual function in patients whose vision loss leads to functional impairment (no need to wait for “ripe” cataract, may postpone surgery as long as one eye has sufficient vision)
    - to aid management of other ocular disease (e.g. cataract that prevents adequate retinal exam or laser treatment of DR)
    - congenital or traumatic cataracts
  - phacoemulsification (phaco = lens)
  - most commonly used surgical technique (see Surgical Ophthalmology, OP44)
  - femtosecond laser for the anterior capsulotomy and fragmentation of the lens
- post-operative complications
  - RD, endophthalmitis, dislocated IOL, macular edema, glaucoma
  - with new foldable IOLs that have truncated edges, <10% of patients get posterior capsular opacification, which should be treated with YAG laser

**Prognosis**
- excellent if not complicated by other ocular disease
**Dislocated Lens (Ectopia Lentis)**

**Etiology**
- associated with Marfan’s Syndrome, Ehlers-Danlos type VI, homocystinuria, syphilis, lens coloboma (congenital cleft due to failure of ocular adnexa to complete growth)
- traumatic

**Clinical Features**
- decreased VA
- may get monocular diplopia
- iridodensis (quivering of iris with movement)
- direct ophthalmoscopy may elicit abnormal red reflex

**Complications**
- cataract, glaucoma, uveitis

**Treatment**
- surgical correction ± lens replacement

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**Vitreous**

- clear gel (99% water plus collagen fibrils, glycosaminoglycans, and hyaluronic acid) that fills the posterior segment of eye
- normally adherent to optic disc, pars plana, and along major retinal blood vessels

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**Posterior Vitreous Detachment**

**Etiology**
- central vitreous commonly shrinks and liquefies with age (syneresis)
- during syneresis, molecules that hold water condense causing vitreous floaters
- liquid vitreous moves between posterior vitreous gel and retina
- vitreous is peeled away and separates from the internal limiting membrane of the neurosensory retina posterior to the vitreous base

**Clinical Features**
- floaters, flashes of light

**Complications**
- traction at areas of abnormal vitreoretinal adhesions may cause retinal tears/detachment
- retinal tears/detachment may cause vitreous hemorrhage if bridging retinal blood vessel is torn
- complications more common in high myopes and following ocular trauma (blunt or perforating)

**Treatment**
- acute onset of PVD requires a dilated fundus exam to rule out retinal tears/detachment
- no specific treatment available for floaters/flashes of light

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**Vitreous Hemorrhage**

- bleeding into the vitreous cavity

**Etiology**
- PDR
- retinal tear/detachment
- PVD
- retinal vein occlusion
- trauma

**Clinical Features**
- sudden loss of VA
- may be preceded by "shower" of many floaters and/or flashes of light
- ophthalmoscopy: no red reflex if large hemorrhage, retina not visible due to blood in vitreous

**Treatment**
- ultrasound (B-scan) to rule out RD
- expectant: in non-urgent cases (e.g. no RD), blood usually resorbs in 3-6 mo
- surgical: vitrectomy ± RD repair ± retinal endolaser to possible bleeding sites/vessels

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**Floaters:** "bugs", "cobwebs", or "spots" of vitreous condensation that change with eye position

**Weiss Ring:** formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous

**Weiss Ring:** formed by glial tissue around the optic disc that remains attached to the detached posterior vitreous

**Vitreous Hemorrhage in a Child:** Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse

Although most floaters are benign, new or markedly increased floaters or flashes of light require a dilated fundus exam to rule out retinal tears/detachment

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**Any time a vitreous or retinal hemorrhage is seen in a child, must rule out child abuse**
**Endophthalmitis and Vitritis**

- intraocular infection: acute, subacute, or chronic

**Etiology**
- most commonly a post-operative complication; risk following cataract surgery is <0.1%
- also due to penetrating injury to eye (risk is 3-7%), endogenous spread, and intravitreal injections
- etiology usually bacterial, may be fungal

**Clinical Features**
- painful, red eye, photophobia, discharge
- severely reduced VA, lid edema, proptosis, corneal edema, anterior chamber cells/flare, hypopyon, reduced red reflex
- may have signs of a ruptured globe (severe subconjunctival hemorrhage, hyphema, decreased IOP, etc.)

**Treatment** (see *Ocular Trauma, OP42*)
- OCULAR EMERGENCY: presenting vision best indicates prognosis
- LP or worse: admission, immediate vitrectomy, and intravitreal antibiotics to prevent loss of vision
- HM or better: vitreous tap for culture and intravitreal antibiotics
- topical fortified antibiotics

**Retina**
- composed of two parts (Figure 2)
  - neurosensory retina: comprises 9 of the 10 retinal layers, including the photoreceptors and the ganglion cell layer
  - retinal pigmented epithelium (RPE) layer: external to neurosensory retina
  - macula: rich in cones (for colour vision); most sensitive area of retina; looks darker due to increased luteal pigment, lack of retinal vessels, and thinning of retina in this region; 15° temporal and slightly below the optic disc
  - fovea: centre of macula; responsible for detail, fine vision
  - optic disc: slightly oval vertically, pinkish colour with centrally depressed yellow cup (normal C:D ratio is ≤0.4), retinal artery and vein pass through cup
  - ora serrata: irregularly-shaped, anterior margin of the retina (can only be visualized with indirect ophthalmoscopy of the far peripheral retina, or through a Goldmann 3 mirror lens)

**Central Retinal Artery Occlusion**

**Etiology**
- emboli from carotid arteries or heart (e.g. arrhythmia, endocarditis, valvular disease)
- thrombus
- temporal arteritis

**Clinical Features**
- sudden, painless (except in GCA), severe monocular loss of vision
- RAPD
- patient may have experienced transient episodes in the past (amaurosis fugax)
- fundoscopy
  - "cherry-red spot"
  - retinal pallor
  - narrowed arterioles, boxcarring (segmentation of blood in arteries)
  - cotton wool spots (retinal infarcts)
  - cholesterol emboli (Hollenhorst plaques) – usually located at arteriole bifurcations
  - after ~6 wk cherry-red spot recedes and optic disc pallor becomes evident

**Treatment**
- OCULAR EMERGENCY: attempt to restore blood flow within 2 h
  - the sooner the treatment = better prognosis (irreversible retinal damage if >90 min of complete CRAO)
  - massage the globe (compress eye with heel of hand for 10 s, release for 10 s, repeat for 5 min) to dislodge embolus
  - decrease IOP
    - topical β-blockers
    - inhaled oxygen-carbon dioxide mixture
    - IV acetazolamide
    - IV mannitol (draws fluid from eye)
    - drain aqueous fluid – anterior chamber paracentesis (carries risk of infection, lens puncture)
    - Nd:YAG laser embolectomy
    - intra-arterial or intra-venous thrombolysis
Branch Retinal Artery Occlusion

- only part of the retina becomes ischemic resulting in a visual field loss
- more likely to be of embolic etiology than CRAO; need to search for source
- management: ocular massage to dislodge embolus if VA is affected

Central/Branch Retinal Vein Occlusion

- second most frequent “vascular” retinal disorder after DR
- usually a manifestation of a systemic disease (e.g. HTN, DM)
- thrombus occurs within the lumen of the blood vessel

Predisposing Factors

- arteriosclerotic vascular disease
- HTN
- DM
- glaucoma
- hyperviscosity (e.g. polycythemia rubra vera, sickle-cell disease, lymphoma, leukemia)
- drugs (e.g. oral contraceptive pill, diuretics)

Clinical Features

- painless, monocular, gradual or sudden vision loss
- ± RAPD
- fundoscopy
  - “blood and thunder” appearance
  - diffuse retinal hemorrhages, cotton wool spots, venous engorgement, swollen optic disc, macular edema
- two fairly distinct groups
  - venous stasis/non-ischemic retinopathy
    - no RAPD, VA ~20/80
    - mild hemorrhage, few cotton wool spots
    - resolves spontaneously over weeks to months
    - may regain normal vision if macula intact
  - hemorrhagic/ischemic retinopathy
    - usually older patient with deficient arterial supply
    - RAPD, VA ~20/200, reduced peripheral vision
    - more hemorrhages, cotton wool spots, congestion
    - poor visual prognosis

Complications

- degeneration of RPE
- neovascularization of retina and iris (secondary rubeosis), leading to secondary glaucoma
- vitreous hemorrhage
- macular edema

Treatment

- no treatment available to restore vision in CRVO/BRVO
- treat underlying cause/contributing factor
- fluorescein angiography to determine extent of retinal non-perfusion (risk of neovascularization)
- retinal laser photocoagulation, or intravitreal anti-VEGF injection to reduce retinal or iris neovascularization and prevent neovascular glaucoma
- macular grid laser photocoagulation for the treatment of macular edema in BRVO, not CRVO, intravitreal or slow-release biodegradable corticosteroid, or anti-VEGF injection is effective in the treatment of macular edema in both CRVO and BRVO

Retinal Detachment

- cleavage in the plane between the neurosensory retina and the RPE
- three types
  - rheumatogenous (most common)
    - caused by a tear or hole in the neurosensory retina, allowing fluid from the vitreous to pass into the subretinal space
    - tears may be caused by PVD, degenerative retinal changes, trauma, or iatrogenically
    - incidence increases with advancing age, in high myopes, and after ocular surgery/truma
  - tractional
    - caused by traction (due to vitreal, epiretinal, or subretinal membrane) pulling the neurosensory retina away from the underlying RPE
    - found in conditions such as DR, CRVO, sickle cell disease, ROP, and ocular trauma
  - exudative
    - caused by damage to the RPE resulting in fluid accumulation in the subretinal space
    - main causes are intraocular tumours, posterior uveitis, central serous retinopathy

Efficacy and Safety of Widely Used Treatments for Macular Oedema Secondary to Retinal Vein Occlusion: A Systematic Review

Purpose: To assess the efficacy of widely used treatments for macular oedema (MO) secondary to retinal vein occlusion (RVO). MO secondary to RVO can cause vision loss due to blockage of the central retinal vein (CRVO) or a branch retinal vein (BRVO).

Outcomes: Mean change in best corrected visual acuity (BCVA) from baseline and/or number of patients gaining at least 10 letters from baseline to 6 mo or equivalent time point.

Results: 14 unique RCTs identified. Ranibizumab 0.5 mg produced greater improvements in BCVA at 6 mo compared to sham in BRVO (mean difference 11 letters; 95% CI 7.83-14.17) and CRVO (mean difference 14 letters; 95% CI 10.51-17.98). Improvements in BCVA were also observed with dexamethasone intravitreal implant (IVT) 0.7 mg compared with sham in patients with BRVO or CRVO (mean difference 2.5 letters; 95% CI 0.7-4.3). The difference was significant with BRVO alone, but not CRVO alone. At 36 mo in a large prospective RCT, a greater proportion of patients with BRVO gained >15 letters with laser therapy versus no treatment (OR 3.16; 95% CI 1.25-8.00), whereas no difference was observed in a 9 mo end point smaller study. Three studies showed no benefit for laser therapy in CRVO.

Conclusions: Both ranibizumab and dexamethasone IVT show significant improvements over previously accepted standard of care (laser therapy) for the treatment of BRVO and CRVO.

The “blood and thunder” appearance on fundoscopy is very characteristic of a CRVO

There is an 8-10% risk of developing CRVO or BRVO in other eye

GENEVA Phase 3 Trials in BRVO and CRVO

Optimally to 117:1134-146
Randomized sham-controlled trial of dexamethasone intravitreal implant in patients with macular edema due to retinal vein occlusion.
Dexamethasone intravitreal implant reduces the risk of vision loss and improves the speed and incidence of visual improvement in eyes with macular edema 2° to BRVO and CRVO.

Superotemporal retina is the most common site for horseshoe tears
Clinical Features
• sudden onset
• flashes of light
  - due to mechanical stimulation of the retinal photoreceptors
• floaters
  - hazy spots in the line of vision which move with eye position, due to drops of blood from torn vessels bleeding into the vitreous
• curtain of blackness/ peripheral field loss
  - darkness in one field of vision when the retina detaches in that area
• loss of central vision (if macula “off”)
• decreased IOP (usually 4-5 mmHg lower than the other, normal eye)
• ophthalmoscopy: detached retina is grey-white with surface blood vessels, loss of red reflex
• ± RAPD

Treatment
• prophylactic: symptomatic tear (floaters or floaters) can be sealed off with laser/cryotherapy, with the goal of preventing progression to detachment
• therapeutic
  - rhegmatogenous
    - scleral buckle procedure (see Surgical Ophthalmology, OP44)
    - pneumatic retinopexy (see Surgical Ophthalmology, OP44)
    - both treatments above are used in combination with localization of retinal tears/holes and subsequent treatment with cryotherapy or laser to create adhesions between the RPE and the neurosensory retina
  - vitrectomy plus injection of gas or silicone oil in cases of recurrent detachment
  - tractional
    - vitrectomy ± membrane removal/scleral buckling/injection of intraocular gas or silicone oil as necessary
  - exudative
  - treat underlying cause

Complications
• loss of vision, vitreous hemorrhage, recurrent RD
• a RD is an emergency, especially if the macula is still attached (macula “on”)
• prognosis for visual recovery varies inversely with the amount of time the retina is detached and whether the macula is attached or not

Retinitis Pigmentosa
• worldwide incidence between 1/3,500 and 1/7,000 people
• many forms of inheritance, most commonly autosomal recessive (60%)
• hereditary degenerative disease of the retina manifested by rod > cone photoreceptor degeneration and retinal atrophy

Clinical Features
• night blindness, decreased peripheral vision (“tunnel vision”), decreased central vision (macular changes), glare (from posterior subcapsular cataracts, common)

Investigations
• fundoscopy: areas of “bone-spicule” pigment clumping in mid-periphery of retina, narrowed retinal arterioles, pale optic disc
• electrophysiological tests: electroretinography (ERG) and electrooculography (EOG) assist in diagnosis

Treatment
• no treatments available to reverse the condition; cataract extraction improves visual function; vitamin A and vitamin E supplementation can reduce progression of disease in some patients

Leber’s Congenital Amaurosis
• worldwide incidence 1/80,000
• inherited degeneration, autosomal recessive

Clinical Features
• symptoms: resting nystagmus, sluggish or no pupillary response, severe vision loss/blindness

Investigations
• diagnosis: 11 types, confirmed by genetic testing

Treatment
• no treatments available to reverse the conditions for most forms; one form (LCA2) shown to be successfully treatable by gene replacement using adeno-associated virus
Age-Related Macular Degeneration

- leading cause of irreversible blindness in the western world, associated with increasing age, usually bilateral
- 10% of people >65 yr old have some degree of AMD
- F>M
- degenerative changes are concentrated at the macula, thus only central vision is lost; peripheral vision (important for navigation) is maintained so patients can usually maintain an independent lifestyle

Classification

- Non-Exudative/“Dry” (Non-Neovascular) AMD
  - most common type of AMD (90% of cases)
  - slowly progressive loss of visual function
  - drusen: yellow-white deposits between the RPE and Bruch’s membrane (area separating inner choroidal vessels from RPE)
  - RPE atrophy: coalescence of depigmented RPE, clumps of focal hyperpigmentation, or hypopigmentation
  - may progress to neovascular AMD

- Exudative/“Wet” (Neovascular) AMD
  - 10% of AMD, but 80% of AMD that results in severe vision loss
  - choroidal neovascularization: drusen predisposes to breaks in Bruch’s membrane causing subsequent growth and proliferation of choroidal capillaries
  - may lead to serous detachment of overlying RPE and retina, hemorrhage and lipid precipitates into subretinal space
  - can also lead to an elevated subretinal mass due to fibrous metaplasia of hemorrhagic RD
  - leads to disciform scarring and severe central vision loss

Risk Factors

- female
- increasing age
- family history
- smoking
- Caucasian race
- blue irides

Clinical Features

- variable degree of progressive central vision loss
- metamorphopsia (distorted vision characterized by straight parallel lines appearing convergent or wavy) due to macular edema

Investigations

- Amsler grid: held at normal reading distance with glasses on, assesses macular function
- fluorescein angiography: assess type and location of choroidal neovascularization – pathologic new vessels leak dye
- OCT retinal imaging

Treatment

- non-neovascular “dry” AMD
  - monitor, Amsler grid allows patients to check for metamorphopsia
  - low vision aids (e.g. magnifiers, closed-circuit television)
  - anti-oxidants, green leafy vegetables
  - sunglasses/visors
  - see Age-related Eye Disease Study (AREDS) and Age-related Eye Disease Study 2 (AREDS2) in sidebar
- neovascular “wet” AMD
  - see Common Medications, OP44
    - intravitreal injection of anti-VEGF
      - pegaptanib (Macugen*), ranibizumab (Lucentis*), bevacizumab (Avastin*), afibercept (Eylea*) (see VEGF Inhibitors, OP45)
    - laser photocoagulation for neovascularization
    - no definitive treatment for disciform scarring
    - PDT with verteporfin (Visudyne*)
      - IV injection of verteporfin followed by low intensity laser to area of choroidal neovascularization
  - see Age-Related Eye Disease Study (AREDS)
  - AREDS studied the effect of high-dose combination of vitamin C, vitamin E, β-carotene, and zinc in patients with and without AMD. Those who are already affected by AMD showed 19% decrease in risk of further visual loss, whereas high dose supplementation showed no benefit in patients with early or no AMD.

Wet AMD Lesions on Fluorescein Angiography

- Classic: well-defined leakage
- Occult: mottled or ill-defined leakage

Drusen vs. Exudate

- Drusen: hyaline material secreted by RPE seen frequently in AMD specifically in perimacular region
- Hard/Soft Exudates: lipid deposits in the retina associated with DR and HTN

Age-Related Eye Disease Study 2 (AREDS2)

  - Addition of lutein + zeaxanthin, DHA + EPA, or both to the AREDS formulation in primary analyses didn’t reduce risk of progression to advanced AMD. However, because of the potential increased incidence of lung cancer in former smokers, lutein + zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation.

Age-Related Macular Degeneration

- CATT Research Group. NEJM 2011;364:1897-1908
  - Study: A multicentre, single-blind, randomized control trial comparing the effects of ranibizumab and bevacizumab on visual acuity in patients with age-related macular degeneration (AMD).
  - Patients: 1,208 patients aged 50 or more with previously untreated AMD and visual acuity between 20/25 and 20/300.
  - Intervention: Intravitreal injections of ranibizumab vs. intravitreal injections of bevacizumab.
  - Results: The monthly use of either bevacizumab or ranibizumab results in the same visual acuity outcome. This finding holds true for the mean visual acuity and the proportion of patients who gain 15 letters, lose 15 letters, or remain stable.
  - Equivalent visual acuity outcomes were observed with both the monthly and the as-needed regimens of ranibizumab.
  - Conclusion: This study supports the use of either bevacizumab or ranibizumab for the treatment of neovascular AMD. The continued global use of intravitreal bevacizumab is an equally effective, low-cost alternative to ranibizumab.

- Intravitreal bevacizumab and ranibizumab for Neovascular Age-Related Macular Degeneration
  - CATT Research Group. NEJM 2011;364:1897-1908
  - Study: A multicentre, single-blind, randomized control trial comparing the effects of ranibizumab and bevacizumab on visual acuity in patients with age-related macular degeneration (AMD).
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  - Conclusion: This study supports the use of either bevacizumab or ranibizumab for the treatment of neovascular AMD. The continued global use of intravitreal bevacizumab is an equally effective, low-cost alternative to ranibizumab.
Glaucoma

Definition
- progressive optic neuropathy involving characteristic structural changes to optic nerve head with associated visual field changes
- commonly associated with high IOP, but not required for diagnosis

Background
- aqueous is produced by the ciliary body and flows from the posterior chamber to the anterior chamber through the pupil, and drains into the episcleral veins via the trabecular meshwork and the Canal of Schlemm
- an isolated increase in IOP is termed OHT (or glaucoma suspect) and these patients should be followed for increased risk of developing glaucoma (10% if IOP 20-30 mmHg; 40% if IOP 30-40 mmHg; and most if IOP >40 mmHg)
- pressures >21 mmHg are more likely to be associated with glaucoma; however, up to 50% of patients with glaucoma do not have IOP >21 mmHg
- loss of peripheral vision most commonly precedes central loss
- sequence of events: gradual pressure rise → increased C:D ratio → visual field loss

Investigations
- medical and family history
- VA testing
- slit-lamp exam to assess anterior chamber depth with gonioscopic lens to assess angle patency
- ophthalmoscopy to assess the disc features
- tonometry by applanation or indentation to measure IOP
- visual field testing
- pachymetry to measure corneal thickness
- future follow-up includes optic disc examination, IOP measurement, and visual field testing to monitor course of disease

Figure 19. Glaucomatous damage

![Figure 19. Glaucomatous damage](image)

Figure 20. Aqueous flow and sites of potential resistance

![Figure 20. Aqueous flow and sites of potential resistance](image)

Ten Year Follow-Up of Age-Related Macular Degeneration in the Age-Related Eye Disease Study: AREDS Report No. 36

Study: Randomized clinical trial.
Objective: To describe 10 yr progression rates to intermediate or advanced AMD.
Patients: Age-related eye disease study (AREDS) participants were observed for an additional 5 yr after RCT completion. Participants aged 55-80 yr with no AMD or AMD of varying severity (n = 4,757) were followed up in the AREDS trial for a median duration of 6.5 yr. When the trial ended, 3,549 of the 4,203 surviving participants were followed for 5 additional yr.
Intervention: Treatment with antioxidant vitamins and minerals.
Main Outcome: Development of varying stages of AMD and changes in visual acuity.
Results: The risk of progression to advanced AMD increased with increasing age (p<0.01) and severity of drusen. Women (p=0.005) and current smokers (p<0.001) were at increased risk of neovascular AMD. In the oldest participants with the most severe AMD status at baseline, the risks of developing neovascular AMD and central geographic atrophy by 10 yr were 46.1% and 26.0%, respectively. Similarly, rates of progression to large drusen increased with increasing severity of drusen at baseline, with 70.9% of participants with bilateral medium drusen progressing to large drusen and 13.8% to advanced AMD in 10 yr. Median visual acuity at 10 yr in eyes that had large drusen at baseline but never developed advanced AMD was 20/25; eyes that developed advanced AMD had a median visual acuity of 20/200.
Conclusion: The natural history of AMD demonstrates relentless loss of vision in persons who developed advanced AMD.

Average IOP = 15 ± 3 mmHg
Normal C:D ≤0.4
Suspect glaucoma if C:D ratio >0.6, C:D ratio differs between eyes by >0.2, or cup approaches disc margin

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Primary Open-Angle Glaucoma

- most common form, >95% of all glaucoma cases
- due to obstruction of aqueous drainage within the trabecular meshwork and its drainage into the Canal of Schlemm
- insidious and asymptomatic, screening is critical for early detection

Major Risk Factors
- elevated IOP (>21 mmHg)
- age: prevalence at 40 yr is 1-2% and at 80 yr is 10%
- ethnicity: African descent
- familial (2-3x increased risk); polygenic
- thin central cornea (OHTS trial)

Minor Risk Factors
- myopia
- HTN
- DM
- hyperthyroidism (Graves’ disease)
- chronic topical ophthalmic steroid use in steroid responders – yearly eye exams recommended if >4 wk of steroid use
- previous ocular trauma
- anemia/hemodynamic crisis (ask about blood transfusions in past)

Clinical Features
- asymptomatic initially
- insidious, painless, gradual rise in IOP due to restriction of aqueous outflow
- bilateral, but usually asymmetric
- earliest signs are optic disc changes
  - increased C:D ratio (vertical C:D >0.6)
  - significant C:D asymmetry between eyes (>0.2 difference)
  - thinning, notching of the neuroretinal rim
  - flame shaped disc hemorrhage
  - 360° of peripapillary atrophy
  - nerve fibre layer defect
  - large vessels become nasally displaced
- visual field loss
  - slow, progressive, irreversible loss of peripheral vision
  - paracentral defects, arcuate scotoma, and nasal step are characteristics (Figure 19)
  - late loss of central vision if untreated

Treatment
- medical treatment: decrease IOP by increasing the drainage and/or decreasing the production of aqueous (see Glaucoma Medications, Table 12, OP45)
  - increase aqueous outflow
    - topical cholinergics
    - topical prostaglandin analogues
    - topical α-adrenergics
  - decrease aqueous production
    - topical β-blockers
    - topical and oral carbonic anhydrase inhibitor
    - topical α-adrenergics
  - laser trabeculoplasty, cyclophotocoagulation in order to achieve selective destruction of ciliary body (for refractory cases)
  - trabeculectomy or minimally invasive glaucoma surgery (MIGS) (see Surgical Ophthalmology, OP44)
  - serial optic nerve head examinations, IOP measurements, and visual field testing to monitor disease course

Normal Tension Glaucoma

- POAG with IOP in normal range
- often found in women >60 but may occur earlier
- associated with migraines, peripheral vasospasm, systemic nocturnal hypotension, sleep apnea
- damage to optic nerve may be due to vascular insufficiency

Treatment
- treat reversible causes
**Secondary Open Angle Glaucoma**

- increased IOP secondary to ocular/systemic disorders that obstruct the trabecular meshwork
  - steroid-induced glaucoma
  - traumatic glaucoma
  - pigmentary dispersion syndrome
  - pseudoexfoliation syndrome

**Primary Angle-Closure Glaucoma**

- 5% of all glaucoma cases
- peripheral iris bows forward in an already susceptible eye with a shallow anterior chamber obstructing aqueous access to the trabecular meshwork
- sudden forward shift of the lens-iris diaphragm causes pupillary block, and results in inability of the aqueous to flow from the posterior chamber to the anterior chamber resulting in a sudden rise in IOP

**Risk Factors**

- hyperopia: small eye, big lens – large lens crowds the angle
- age >70 yr
- female
- family history
- more common in people of Asian and Inuit descent
- mature cataracts
- shallow anterior chamber
- pupil dilation (topical and systemic anticholinergics, stress, darkness)

**Clinical Features**

- red, painful eye = RED FLAG
- unilateral, but other eye increased risk
- decreased visual acuity, vision acutely blurred from corneal edema
- halos around lights
- nausea and vomiting, abdominal pain
- fixed, mid-dilated pupil
- corneal edema with conjunctival injection
- marked increase in IOP; may be noticeable even to palpation (>40 mmHg)
- shallow anterior chamber ± cells in anterior chamber

**Complications**

- irreversible loss of vision within hours to days if untreated
- permanent peripheral anterior synechiae, resulting in permanent angle closure

**Treatment**

- **OCULAR EMERGENCY:** refer to ophthalmologist for acute angle closure glaucoma
  - aqueous suppressants and hyperosmotic agents
  - medical treatment (see Glaucoma Medications, Table 12, OP45)
    - miotic drops (pilocarpine) to reverse pupillary block
    - decrease IOP
      - topical β-blockers
      - topical adrenergics
      - topical cholinergics
        - pilocarpine 1-4% q15min, up to q5min
      - systemic carbonic anhydrase inhibitors
        - IV acetazolamide 250-500 mg
      - systemic hyperosmotic agents
        - oral glycerine 1 g/kg
        - IV mannitol 1 g/kg
      - laser iridotomy

**Secondary Angle-Closure Glaucoma**

**Uveitis**

- inflamed iris adheres to lens (posterior synechiae)

**Neovascular Glaucoma**

- abnormal blood vessels develop on surface of iris (rubeosis iridis), in the angle, and within the trabecular meshwork
- due to retinal ischemia associated with PDR or CRVO
- treatment with laser therapy to retina reduces neovascular stimulus to iris vessels

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**Rule of Fours**

1/4 of general population using topical steroid for 4 wk, 4 x/d will develop an increase in IOP

**Collaborative Normal Tension Glaucoma Study**

**Cochrane systematic review of 26 trials and meta-analysis of 10 trials investigating the effectiveness of topical pharmacological therapies for POAG or OHT.**

- Patients: 4,979 participants randomized in 26 trials. Patients had OHT with IOP >21 mmHg or open angle glaucoma.
- Intervention: Topical eye medications, including β-blockers, dorzolamide, brimonidine, pilocarpine, and epinephrine vs. each other and placebo.
- Main Outcome: Reduction of progression or prevention of onset of visual field defects.
- Results: Meta-analysis on all trials that tested drops against placebo or untreated controls demonstrated that lowering IOP reduces incidence of glaucomatous visual field defects, with an odds ratio of 0.62 (95% CI 0.47-0.81). However, this result is of limited practical use since different therapies were pooled. No single drug demonstrated significant visual field protection.
- Conclusion: Lowering IOP cannot prevent progression of visual field defects in patients with OHT.
Pupils

• pupil size is determined by the balance between the sphincter muscle and the dilator muscle
  • sphincter muscle is innervated by the parasympathetic nervous system
    ▪ carried by CN III: pre- and post-ganglionic fibres synapse in ciliary ganglion, and use acetylcholine as the neurotransmitter
  • dilator muscle is innervated by the sympathetic nervous system (SNS)
    ▪ first order neuron = hypothalamus → brainstem → spinal cord
    ▪ second order/preganglionic neuron = spinal cord → sympathetic trunk via internal carotid artery → superior cervical ganglion in neck
    ▪ third order/postganglionic fibres originate in the superior cervical ganglion, neurotransmitter is norepinephrine
      • as a diagnostic test, 4-10% cocaine prevents the re-uptake of norepinephrine, and will cause dilation of normal pupil, but not one with loss of sympathetic innervation (Horner's Syndrome)
      • see Neurology, Figure 8, N8

Pupillary Light Reflex

• light shone directly into eye travels along optic nerve (CN II, afferent limb) → optic tracts → bilateral midbrain
• impulses enter bilaterally in midbrain via pretectal area and Edinger-Westphal nuclei
• nerve impulses then travel down CN III (efferent limb) bilaterally to reach the ciliary ganglia, and finally to the iris sphincter muscle, which results in the direct and consensual light reflexes
  α1 – Pupillary dilator muscle contraction (Mydriasis)
  β2 – Ciliary muscle relaxation (Non-accommodation); increased aqueous humor production
  M3 – Pupillary sphincter contraction (Miosis); increased ciliary muscle contraction (Accommodation)

Pupil Abnormalities

Denervation Hypersensitivity
• when post-ganglionic fibers are damaged, the understimulated end-organ attempts to compensate by developing an excess of neuroreceptors and becomes hypersensitive
• postganglionic parasympathetic lesions (i.e. Adie's pupil)
  ▪ pupil will constrict with 0.125% pilocarpine (cholinergic agonist), normal pupil will not
• postganglionic sympathetic lesions (this test is used to differentiate between pre- and post-ganglionic lesions in Horner's syndrome)
  ▪ pupil will dilate with 0.125% epinephrine, normal pupil will not

Local Disorders of Iris
• posterior synechiae (adhesions between iris and lens) due to iritis can present as an abnormally shaped pupil
• ischemic damage (e.g. post-acute angle-closure glaucoma) usually occurs at 3 and 9 o'clock positions resulting in a vertically oval pupil that reacts poorly to light
• trauma (e.g. post-intraocular surgery)

Anisocoria
• unequal pupil size
• idiopathic/physiologic anisocoria
  ▪ 20% of population
  ▪ round, regular, <1 mm difference
  ▪ pupils reactive to light and accommodation
  ▪ responds normally to mydriatics/miotics
• post eye surgery
• see Table 7 for other causes of anisocoria

5 Targets of Retinal Signals
• Pre-tectal nucleus (pupillary reflex/eye movements)
• Lateral geniculate body of thalamus
• Superior colliculus (eye movements)
• Suprachiasmatic nucleus (optokinetic)
• Accessory optic system (circadian rhythm)
**Table 7. Summary of Conditions Causing Anisocoria**

<table>
<thead>
<tr>
<th>Features</th>
<th>Site of Lesion</th>
<th>Light and Accommodation</th>
<th>Anisocoria</th>
<th>Mydriatics/Miotics</th>
<th>Effect of Pilocarpine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABNORMAL MIOTIC PUPIL (impaired pupillary dilation)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Argyll-Robertson Pupil</td>
<td>Irregular, usually bilateral</td>
<td>Midbrain</td>
<td>Poor in light; better to accommodation</td>
<td>Attend pupil dilates</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td>Horner’s Syndrome</td>
<td>Round, unilateral, ptosis, anhydrosis, pseudoenophthalmos</td>
<td>Sympathetic system</td>
<td>Both brisk</td>
<td>Greater in dark</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td><strong>ABNORMAL MYDRIATIC PUPIL (impaired pupillary constriction)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adie’s Tonic Pupil</td>
<td>Irregular, larger in bright light</td>
<td>Ciliary ganglion</td>
<td>Poor in light, better to accommodation</td>
<td>Greater in light</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td>CN III Palsy</td>
<td>Round</td>
<td>Superficial CN III</td>
<td>± fixed (acutely) at 7-9 mm</td>
<td>Greater in light</td>
<td>Dilates/Constricts</td>
</tr>
<tr>
<td>Mydriatic Pupil</td>
<td>Round, uni- or bilateral</td>
<td>Iris sphincter</td>
<td>Fixed at 7-8 mm</td>
<td>Greater in light</td>
<td>No effect</td>
</tr>
</tbody>
</table>

**Figure 22. Approach to anisocoria**
Dilated Pupil (Mydriasis)

**Sympathetic Stimulation**
- fight or flight response
- mydriatic drugs: epinephrine, dipivefrin (Propine®), phenylephrine

**Parasympathetic Understimulation**
- cycloplegics/mydriatics: atropine, tropicamide, cyclopentolate (parasympatholytic)
- CN III palsy
  - eye deviated down and out with ptosis present
  - etiology includes stroke, neoplasm, aneurysm, acute rise in ICP, DM (may spare pupil), trauma
  - CN III palsy will respond to drugs (e.g. pilocarpine), unlike a pupil dilated from medication (mydriatics)

**Acute Angle-Closure Glaucoma**
- fixed, mid-dilated pupil

**Adie's Tonic Pupil**
- 80% unilateral, F>M
- pupil is tonic or reacts poorly to light (both direct and consensual) but constricts with accommodation
- if decreased deep tendon reflexes may be Adie's syndrome
- caused by benign lesion in ciliary ganglion; results in denervation hypersensitivity of parasympathetically innervated constrictor muscle
  - dilute (0.125%) solution of pilocarpine will constrict tonic pupil but have no effect on normal pupil
- long-standing Adie's pupils are smaller than unaffected eye

**Trauma**
- damage to iris sphincter from blunt or penetrating trauma
- iris transillumination defects may be apparent using ophthalmoscope or slit-lamp
- pupil may be dilated (traumatic mydriasis) or irregularly shaped from tiny sphincter ruptures

Constricted Pupil (Miosis)

**Senile Miosis**
- decreased sympathetic stimulation with age

**Parasympathetic Stimulation**
- local or systemic medications such as:
  - cholinergic agents: pilocarpine, carbachol
  - cholinesterase inhibitor: phospholine iodide
  - opiates, barbiturates

**Horner's Syndrome**
- lesion in sympathetic pathway
- difference in pupil size greater in dim light, due to decreased innervation of adrenergics to iris dilator muscle
- associated with ptosis, anhydrosis of ipsilateral face/neck
- application of cocaine 4-10% (blocks reuptake of norepinephrine) to eye does not result in pupil dilation (vs. physiologic anisocoria), therefore confirms diagnosis
- hydroxyamphetamine 1% (stimulates norepinephrine release) will dilate pupil if central or preganglionic lesion, not postganglionic lesion
- postganglionic lesions result in denervation hypersensitivity, which will cause pupil to dilate with 0.125% epinephrine, whereas normal pupil will not
- causes: carotid or subclavian aneurysm, brainstem infarct, demyelinating disease, cervical or mediastinal tumour, Pancoast tumour, goitre, cervical lymphadenopathy, surgical sympathectomy, Lyme disease, cervical ribs, tabes dorsalis, cervical vertebral fractures

**Iritis**
- miotic pupil initially
- later, may be irregularly shaped pupil due to posterior synechiae
- later stages non-reactive to light
Argyll-Robertson Pupil
• both pupils irregular and <3 mm in diameter, ± ptosis
• does not respond to light stimulation
• responds to accommodation (light-near dissociation)
• suggestive of neurosyphilis or other conditions (DM, encephalitis, MS, chronic alcoholism, CNS degenerative diseases)

Other Causes
• optic neuritis, retinal lesions

Relative Afferent Pupillary Defect

- also known as Marcus Gunn pupil
- impairment of direct pupillary response to light, caused by a lesion in visual afferent (sensory) pathway anterior to optic chiasm
- differential diagnosis: large RD, BRAO, CRAO, CRVO, advanced glaucoma, optic nerve compression, optic neuritis (most common)
- does not occur with media opacity (e.g. corneal edema, cataracts)
- pupil reacts poorly to light and better to accommodation
- test: swinging flashlight
  - if light is shone in the affected eye, direct and consensual response to light is decreased
  - if light is shone in the unaffected eye, direct and consensual response to light is normal
  - if the light is moved quickly from the unaffacted eye to the affected eye, “paradoxical” dilation of both pupils occurs
  - observe red reflex, especially in patients with dark irides
- if the defect is bilateral there is no RAPD, as dilation is measured relative to the other eye
Malignancies

- uncommon site for 1° malignancies
- eye usually affected secondarily by cancer or cancer treatments
- see Retinoblastoma, OP41

Lid Carcinoma

Etiology
- basal cell carcinoma (rodent ulcer) (90%)
  - spread via local invasion, rarely metastasizes
  - ulcerated centre, indurated base with pearly rolled edges, telangiectasia
- squamous cell carcinoma (<5%)
  - spread via local invasion, may also spread to nodes and metastasize
  - ulceration, keratosis of lesion
- sebaceous cell carcinoma (1-5%)
  - often masquerades as chronic blepharitis or recurrent chalazion
  - highly invasive, metastasize
  - Kaposi's sarcoma, malignant melanoma, Merkel cell tumour, metastatic tumour

Treatment
- incisional or excisional biopsies
- may require cryotherapy, radiotherapy, chemotherapy, immunotherapy
- surgical reconstruction

Malignant Melanoma

- most common 1° intraocular malignancy in adults
- more prevalent in Caucasians
- arise from uveal tract, 90% choroidal melanoma
- hepatic metastases predominate

Treatment
- imaging to investigate spread
- depending on the size of the tumour, either radiotherapy, enucleation, limited surgery

Metastases

- most common intraocular malignancy in adults
- most commonly from breast and lung in adults, neuroblastoma in children
- usually infiltrate the choroid, but may also affect the optic nerve or extraocular muscles
- may present with decreased or distorted vision, irregularly shaped pupil, iritis, hyphema

Treatment
- local radiation, chemotherapy
- enucleation if blind, painful eye

Ocular Manifestations of Systemic Disease

HIV/AIDS

- up to 75% of patients with AIDS have ocular manifestations

External Ocular Signs
- Kaposi's sarcoma
  - secondary to human herpes virus 8 (HHV-8), affects conjunctiva of lid or globe
  - numerous vascular skin malignancies
  - differential diagnosis: subconjunctival hemorrhage (non-clearing), hemangioma
- multiple molluscum contagiosum
- herpes simplex keratitis
- herpes zoster keratitis
Retina
- HIV retinopathy (most common)
  - cotton wool spots in >50% of HIV patients
  - intraretinal hemorrhage
- CMV retinitis
  - ocular opportunistic infection that develops in late stages of HIV when severely immunocompromised (CD4 count ≤50)
  - a necrotizing retinitis, with retinal hemorrhage and vasculitis, “brushfire” or “pizza pie” appearance
  - presents with scotomas (macular involvement and RD), blurred vision, and floaters
  - untreated infection will progress to other eye in 4-6 wk
  - treatment: virostatic agents (e.g. gancyclovir or foscarnet) via IV or intravitreal injection
- necrotizing retinitis
  - from herpes simplex virus, herpes zoster, toxoplasmosis
- disseminated choroiditis
  - *Pneumocystis carinii, Mycobacterium avium intracellulare, Candida*

Other Systemic Infections
- herpes zoster
  - see *Herpes Zoster, OP19*
- candidal endophthalmitis
  - fluffy, white-yellow, superficial retinal infiltrate that may eventually result in vitritis
  - may present with inflammation of the anterior chamber
  - treatment: systemic amphotericin B, oral fluconazole
- toxoplasmosis
  - focal, grey-yellow-white, chorioretinal lesions with surrounding vasculitis and vitreous infiltration (vitreous cells)
  - can be congenital (transplacental) or acquired (caused by *Toxoplasma gondii* protozoa transmitted through raw meat and cat feces)
  - congenital form more often causes visual impairment (more likely to involve the macula)
  - treatment: pyrimethamine, sulfonamide, folic acid, or clindamycin. Consider adding steroids if severe inflammation (vitritis, macular or optic nerve involvement)

Diabetes Mellitus
- see *Endocrinology, E7*
- most common cause of blindness in young people in North America
- consider DM if unexplained retinopathy, cataract, extraocular muscle palsy, optic neuropathy, sudden change in refractive error
- loss of vision due to
  - progressive microangiopathy leading to macular edema
  - progressive DR → neovascularization → traction → RD and vitreous hemorrhage
  - rubecosis iridis (neovascularization of the iris) leading to neovascular glaucoma (poor prognosis)
  - macular ischemia

DIABETIC RETINOPATHY

Background
- altered vascular permeability (loss of pericytes, breakdown of blood-retinal barrier, thickening of basement membrane)
- predisposition to retinal vessel obstruction (CRAO, CRVO, and BRVO)

Classification
- non-proliferative: increased vascular permeability and retinal ischemia
  - microaneurysms
  - dot and blot hemorrhages
  - hard exudates (lipid deposits), non-specific for DR
  - macular edema
- advanced non-proliferative (or pre-proliferative)
  - non-proliferative findings plus:
    - venous beading (in ≥2 of 4 retinal quadrants)
    - intraretinal microvascular anomalies (IRMA) in 1 of 4 retinal quadrants
      - IRMA: dilated, leaky vessels within the retina
    - cotton wool spots (nerve fibre layer infarcts)
- proliferative
  - 5% of patients with DM will reach this stage
- neovascularization of iris, disc, retina to vitreous
- neovascularization of iris (rubeosis iridis) can lead to neovascular glaucoma
- vitreous hemorrhage from bleeding, fragile new vessels, fibrous tissue can contract causating tractional RD
- high risk of severe vision loss secondary to vitreous hemorrhage, RD

Screening Guidelines for Diabetic Retinopathy
- type 1 DM
  - screen for retinopathy beginning annually 5 yr after disease onset
  - annual screening indicated for all patients over 12 yr and/or entering puberty
- type 2 DM
  - initial examination at time of diagnosis, then annually
- pregnancy
  - ocular exam in 1st trimester, close follow-up throughout as pregnancy can exacerbate DR
- gestational diabetics are not at risk for DR

Treatment
- Diabetic Control and Complications Trial (DCCT)
- tight control of blood sugar decreases frequency and severity of microvascular complications
- blood pressure control
- focal laser for clinically significant macular edema
- intravitreal injection of corticosteroid or anti-VEGF for foveal involved diabetic macular edema
- panretinal laser photocoagulation for PDR: reduces neovascularization, hence reducing the angiogenic stimulus from ischemic retina by decreasing retinal metabolic demand → reduces risk of blindness
- vitrectomy for non-clearing vitreous hemorrhage and tractional RD in PDR

Lens Changes
- earlier onset of senile nuclear sclerotic and cortical cataracts
- may get hyperglycemic cataract, due to sorbitol accumulation (rare)
- changes in blood glucose levels (poor control) can suddenly cause refractive changes by 3-4 diopters

Extraocular Muscle Palsy
- usually CN III infarct
- pupil usually spared in diabetic CN III palsy, but ptosis is observed
- may involve CN IV and VI
- usually recover within few months

Optic Neuropathy
- visual acuity loss due to infarction of optic disc/nerve

![Figure 25. DM vs. HTN retinopathy](image-url)
Hypertension

- retinopathy is the most common ocular manifestation
- chronic HTN retinopathy: arteriovenous (AV) nicking, blot retinal hemorrhages, microaneurysms, cotton wool spots
- acute HTN retinopathy: retinal arteriolar spasm, superficial retinal hemorrhage, cotton wool spots, optic disc edema

<table>
<thead>
<tr>
<th>Table 8. Keith-Wagener-Barker Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Group 3</td>
</tr>
<tr>
<td>Group 4</td>
</tr>
</tbody>
</table>

Multiple Sclerosis

- see Neurology, N54

Clinical Features

- blurred vision and decreased colour vision: secondary to optic neuritis
- central scotoma: due to damage to papillomacular bundle of retinal nerve fibres
- diplopia: secondary to INO
- RAPD, ptosis, nystagmus, uveitis, optic atrophy, optic neuritis
- white matter demyelinating lesions of optic nerve on MRI

Treatment

- IV steroids with taper to oral form for optic neuritis
  - DO NOT treat with oral steroids in isolation as this increases likelihood of eventual development of MS

TIA/Amaurosis Fugax

- sudden, transient blindness from intermittent vascular compromise
- ipsilateral carotid most frequent embolic source
- typically monocular, lasting <5-10 min
- Hollenhorst plaques (glistening microemboli seen at branch points of retinal arterioles)

Graves’ Disease

- ophthalmopathy occurs despite control of thyroid gland status
- ocular manifestations occur secondary to sympathetic overdrive and/or specific inflammatory infiltrate of the orbital tissue

Clinical

- initial inflammatory phase is followed by a quiescent cicatricial phase

Treatment

- treat hyperthyroidism
- monitor for corneal exposure and maintain corneal hydration
- manage diplopia, ptosis and compressive optic neuropathy with one or a combination of:
  - steroids (during acute phase)
  - orbital bony decompression
  - external beam radiation of the orbit
- consider strabismus and/or eyelid surgical procedures once acute phase subsides

Connective Tissue Disorders

- RA, juvenile idiopathic arthritis, SLE, Sjögren syndrome, ankylosing spondylitis, polyarteritis nodosa
- most common ocular manifestation: dry eyes (keratoconjunctivitis sicca)
**Giant Cell Arteritis/Temporal Arteritis**

- see Rheumatology, RH20

**Clinical Features**
- more common in women >60 yr
- abrupt monocular loss of vision, pain over the temporal artery, jaw claudication, scalp tenderness, constitutional symptoms, and past medical history of polymyalgia rheumatica
- ischemic optic atrophy
  - 50% lose vision in other eye if untreated

**Diagnosis**
- temporal artery biopsy + increased ESR (ESR can be normal, but likely 80-100 in first hour), increased CRP
- if biopsy of one side is negative, biopsy the other side

**Treatment**
- high dose corticosteroid to relieve pain and prevent further ischemic episodes
- if diagnosis of GCA is suspected clinically: start treatment + perform temporal artery biopsy to confirm diagnosis within 2 wk of initial presentation (DO NOT WAIT TO TREAT)

**Sarcoidosis**

- granulomatous uveitis with large "mutton fat" keratitic precipitates and posterior synechiae
- neurosarcoidosis: optic neuropathy, oculomotor abnormalities, visual field loss

**Treatment**
- steroids and mydriatics

**Pediatric Ophthalmology**

**Strabismus**

- ocular misalignment in one or both eyes, found in 3% of children
- object not visualized simultaneously by fovea of each eye
- terms used to describe strabismus depend upon
  - direction of deviation relative to the correctly fixing eye
  - conditions under which it presents: 'latent', 'manifest' misalignment
  - change with the position of gaze: 'comitant' (usually nonparalytic), 'incomitant' (usually occurs with paralytic or restrictive strabismus)
- often presents with parental concern about a wandering eye, crossing eye, or poor vision
- elicit a detailed family history of strabismus, amblyopia, type of eyeglasses and history of wear, extraocular muscle surgery or other eye surgery, and genetic diseases to identify children at higher risk
- distinguish from pseudostrabismus (prominent epicantial folds, hypertelorism, markedly positive or negative angle κ)
- complications: amblyopia, cosmesis

**HETEROTROPIA**

- manifest deviation
- deviation not corrected by the fusion mechanism (i.e. deviation is apparent when the patient is using both eyes)

**Types**

- exo- (lateral deviation), eso- (medial deviation)
- hyper- (upward deviation), hypo- (downward deviation)
- esotropia = "crossed-eyes"; exotropia = "wall-eyed"

**Differentiate from Pseudostrabismus**

- prominent epicantial folds: give appearance of esotropia but Hirschberg test is normal, more common in Asians
- markedly elevated angle κ (the angle formed by the pupillary axis and the visual axis at the centre of the pupil)
  - caused by the failure of optical axis of the eye and the visual axis to coincide
  - a small positive (up to 5°) angle κ is physiologic
  - a large positive angle κ (nasally deviated fovea) simulates eso-appearance
  - a large negative angle κ (temporally deviated fovea) gives an exo-appearance
Tests
- Hirschberg test (corneal light reflex): positive if the light reflex on both corneas is asymmetrical
  - light reflex lateral to central cornea indicates esodeviation; light reflex medial to central cornea indicates exodeviation
  - false positives occur if visual axis and anatomic pupillary axis of the eye are not aligned (angle $\kappa$)
- cover test
- the deviation can be quantified using prisms

HETEROPHORIA
- latent deviation
- deviation corrected in the binocular state by the fusion mechanism (i.e. deviation not seen when patient is focusing with both eyes)
- Hirschberg test will be normal (light reflex symmetrical)
- very common – majority are asymptomatic
- may be exacerbated or become manifest with asthenopia (eye strain, fatigue)

Tests
- cover-uncover test
- alternate cover test
  - alternating the cover between both eyes reveals the total deviation, both latent and manifest
  - maintain cover over one eye for 2-3 s before rapidly shifting to other eye

Table 9. Paralytic vs. Non-Paralytic Strabismus

<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>Paralytic Strabismus</th>
<th>Nonparalytic Strabismus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Incomitant strabismus</td>
<td>Concomitant strabismus</td>
</tr>
<tr>
<td>Onset</td>
<td>Often sudden but may be gradual or congenital</td>
<td>Usually gradual or shortly after birth; rarely sudden</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>Any age; most often acquired</td>
<td>Usually during infancy</td>
</tr>
<tr>
<td>Etiology</td>
<td>Reduction or restriction in range of eye movements due to:</td>
<td>Develops early in childhood</td>
</tr>
<tr>
<td></td>
<td>• Neural (CN III, IV, VI): ischemia (e.g. DM), MS, aneurysm, brain tumour, trauma</td>
<td>No restriction in range of eye movements</td>
</tr>
<tr>
<td></td>
<td>• Muscular: myasthenia gravis (neuromuscular junction pathology), Graves’ disease</td>
<td>Monocular, alternating, or intermittent</td>
</tr>
<tr>
<td></td>
<td>• Structural: restriction or entrapment of extraocular muscles due to orbital inflammation, tumour, fracture of the orbital wall</td>
<td></td>
</tr>
<tr>
<td>Diplopia</td>
<td>Common</td>
<td>Uncommon; image from the misaligned eye is suppressed (see Amblyopia, OP40)</td>
</tr>
<tr>
<td>Visual Acuity in Other Eye</td>
<td>Usually unaffected in the other eye, unless CN II is involved</td>
<td>Deviated eye may become amblyopic if not treated when the child is young</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Amblyopia usually does not develop if child has alternating strabismus or intermittency, which allows neural pathways for both eyes to develop</td>
</tr>
<tr>
<td>Possibility of Amblyopia</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Neurologic Findings or Systemic Disease</td>
<td>May be present</td>
<td>Usually absent</td>
</tr>
</tbody>
</table>
Accommodative Esotropia
- normal response to approaching object is the triad of the near reflex: convergence, accommodation and miosis
- hyperopes must constantly accommodate – excessive accommodation can lead to esotropia in young children via over-activation of the near reflex
- average age of onset is 2.5 yr
- usually reversible with correction of refractive error

Non-accommodative Esotropia
- accounts for 50% of childhood strabismus
- most are idiopathic
- may be due to monocular visual impairment (e.g. cataract, corneal scarring, anisometropia, retinoblastoma) or divergence insufficiency (ocular misalignment that is greater at distance fixation than at near fixation)

Amblyopia

Definition
- a neurodevelopmental visual disorder with unilateral (or less commonly, bilateral) reduction of best corrected visual acuity that cannot be attributed only and directly to the effect of a structural abnormality of the eye. It is caused by abnormal visual experience early in life and cannot be remedied immediately by spectacle glasses alone
- in approximately half of the cases, amblyopia is secondary to strabismus (mainly esotropia). Other causes may include uncorrected refractive errors, anisometropia (asymmetric refractive errors), and concomitant structural ocular problems

Detection
- “Holler Test”: young child upset if good eye is covered
- quantitative visual acuity by age 3-4 yr using picture charts and/or matching game (Sheridan-Gardiner), testing each eye separately
- amblyopia treatment less successful after age 8-10 yr, but a trial should be given no matter what age
- prognosis: 90% will have good vision restored and maintained if treated <4 yr old

Etiology and Management
- strabismus
  - correct with glasses for accommodative esotropia (50% of children experience relief of their esotropia with glasses and will not require surgery)
  - occlusion of unaffected eye forces brain to use previously strabismic eye; aims to bring vision in previously suppressed eye to normal before surgery
  - surgery: recession (weakening) – moving muscle insertion further back on the globe; or resection (strengthening) – shortening the muscle
  - botulinum toxin for single muscle weakening
  - after ocular alignment is restored (glasses, surgery, botulinum toxin), patching is frequently necessary to maintain vision until ~8 yr of age
- anisometropia
  - amblyopia usually in the more hyperopic eye
  - the more emmetropic (normal refraction) eye receives a clear image while the less emmetropic eye receives a blurred image; input from the blurred eye is cortically suppressed and visual pathway fails to develop normally
  - treat with glasses to correct refractive error
  - patching is required if visual acuity difference persists after 4-8 wk of using glasses
- deprivation amblyopia
  - occlusion due to ptosis, cataract, retinoblastoma, corneal opacity
  - occlusion amblyopia: prolonged patching of good eye may cause it to become amblyopic

Occlusion Therapy
- patching the good eye to force the brain to use the non-dominant eye and redevelop its vision
- atropine cycloplegic drops to impair accommodation and blur vision of the better seeing eye

Risks
- permanent loss of vision in the affected eye
- possibility of injury to ‘remaining’ good eye
  - safety glasses or polycarbonate lenses recommended if visual acuity in worse eye is <20/50
- loss of stereopsis
Leukocoria

- white reflex (red reflex is absent)

Differential Diagnosis
- cataract
- retinoblastoma
- retinal coloboma
- ROP
- persistent hyperplastic primary vitreous
- Coats' disease (exudative retinal telangiectasis)
- toxocariasis
- RD

Retinoblastoma

- most common primary intraocular malignancy in children
- incidence: 1/15,000; sporadic or genetic transmission; screening of siblings/offspring essential
- unilateral (2/3) or bilateral (1/3)
- malignant – direct or hematogenous spread
- diagnosis
  - often presents with leukocoria or strabismus
  - U/S or CT scan may demonstrate calcified mass (present in most cases)

Treatment
- radiotherapy, chemotherapy combined with laser, cryopexy, and/or enucleation

Retinopathy of Prematurity

- vasoproliferative retinopathy that is a major cause of blindness in the developed world

Risk Factors
- non-black race (black infants have lower risk of developing ROP)
- low gestational age, birth weight <1500 g
- high oxygen exposure after birth (iatrogenic)

Classification (ROP Staging)
- stage 1: faint demarcation line at the junction between the vascularized and avascular retina
- stage 2: elevated ridge
- stage 3: extra-retinal fibrovascular tissue extending into vitreous
- stage 4: partial RD (4A: macula "on", 4B: macula "off")
- stage 5: total RD
- plus (+) disease: dilatation and tortuosity of retinal vessels
- threshold disease: stage 3+ in zones 1 or 2 with 5 continuous or 8 cumulative clock hours of ROP involvement

Treatment
- threshold disease is treated with cryotherapy or laser (laser is now the standard treatment, with better refractive outcome), off label anti-VEGF intravitreal injections
- ROP beyond threshold level is either watched carefully (usually stage 4A) or treated with vitrectomy/scleral buckle

Prognosis
- higher incidence of myopia among ROP infants, even if treated successfully
- stage 4B and 5 have poor prognosis for visual outcome despite treatment

Nasolacrimal System Defects

- congenital obstruction of the nasolacrimal duct (failure of canalization), usually occurs at 1-2 mo of age
- epiphora, crusting, discharge, recurrent conjunctivitis
- can have reflux of mucopurulent material from lacrimal punctum when pressure is applied over lacrimal sac

Treatment
- massage over lacrimal sac at medial corner of eyelid
- vast majority spontaneously resolve in 9-12 mo, otherwise consider referral for duct probing
**Ophthalmia Neonatorum**

- newborn conjunctivitis in first mo of life
- causes
  - toxic: silver nitrate, erythromycin
  - infectious: bacterial (e.g. *N. gonorrhoeae* – most common, *C. trachomatis*), herpes simplex virus
- diagnose using stains and cultures

**Treatment**

- systemic antibiotics with possible hospitalization if infectious etiology
- topical prophylaxis, most commonly with erythromycin (or silver nitrate), is required by law at birth

**Congenital Glaucoma**

- due to inadequate development of the filtering mechanism of the anterior chamber angle

**Clinical Features**

- cloudy cornea, increased IOP
- photophobia, epiphora
- buphthalmos (large cornea, “ox eye”, secondary to increased IOP), blepharospasm

**Treatment**

- filtration surgery is required soon after birth to prevent blindness

**Ocular Trauma**

**Blunt Trauma**

- caused by blunt object such as fist, squash ball
- history: injury, ocular history, drug allergy, tetanus status
- exam: VA first, pupil size and reaction, EOM (diplopia), external and slit-lamp exam, ophthalmoscopy
- if VA normal or slightly reduced, globe less likely to be perforated
- if VA reduced may be perforated globe, corneal abrasion, lens dislocation, retinal tear
- bone fractures
  - blow out fracture: restricted EOM, diplopia, enophthalmos (sunken eye)
  - ethmoid fracture: subcutaneous emphysema of lid
- lids: swelling, laceration, emphysema
- conjunctiva: subconjunctival hemorrhage
- cornea: abrasion – detect with fluorescein staining and cobalt blue filter using slit-lamp or ophthalmoscope
- anterior chamber: assess depth, hyphema, hypopyon
- iris: prolapse, iritis
- lens: cataract, dislocation
- retinal tear/detachment

**Penetrating Trauma**

- include ruptured globe ± prolapsed iris, intraocular foreign body
- rule out intraocular foreign body, especially if history of “metal striking metal”, orbit CT
- **OCULAR EMERGENCY**: initial management - REFER IMMEDIATELY
  - ABCs
  - don't press on eye globe!
  - don't check IOP if possibility of globe rupture
  - check vision, diplopia
  - apply rigid eye shield to minimize further trauma
  - keep head elevated 30-45° to keep IOP down
  - keep NPO
  - tetanus status
  - give IV antibiotics
  - selecting appropriate agents depends on the mechanism of injury; gram positive bacteria are more commonly involved than gram negatives; retained intraocular foreign objects increase the risk of infections with *Bacillus* species, whereas exposure to vegetable matter increased the risk of a fungal etiology

**Post-Traumatic Infectious Endophthalmitis**

- *Surv Ophthalmol* 2011;56:214-251
- Decreased VA
- Shallow anterior chamber
- Hyphema
- Abnormal pupil
- Ocular misalignment
- Retinal damage

**Management of Suspected Globe Rupture**

- CAN’T forget
  - **C**T orbits
  - **A**ncef (cefazolin) ± **A**minoglycoside IV
  - **N**PO
  - **T**etanus status

- Post-traumatic endophthalmitis in the absence of an intraocular foreign body (IOFB).
- If IOFB present, early vitrectomy and IOFB removal must be performed within 24 h of injury.
- Extreme pain with hypopyon and vitritis indicate endophthalmitis until proven otherwise, and samples must be obtained.
- Treat with empirical intravitreal and intravenous antibiotic guided by nature of trauma, and adjust based on culture.
Hyphema

• blood in anterior chamber often due to damage to root of the iris
• may occur with blunt trauma

Treatment

• refer to ophthalmology
  ▪ shield and bedrest for 5 d or as determined by ophthalmologist
  ▪ sleep with head upright
• may need surgical drainage if hyphema persists or if re-bleed

Complications

• risk of re-bleed highest on days 2-5, resulting in secondary glaucoma, corneal staining, and iris necrosis
• never prescribe Aspirin®, as it increases the risk of a re-bleed

Blow-Out Fracture

• see Plastic Surgery, PL32
• blunt trauma causing fracture of orbital floor and herniation of orbital contents into maxillary sinus
• orbital rim remains intact
• inferior rectus and/or inferior oblique muscles may be incarcerated at fracture site
• infraorbital nerve courses along the floor of the orbit and may be damaged

Clinical Features

• pain and nausea at time of injury
• diplopia, restriction of EOM
• infraorbital and upper lip paresthesia (CN V2)
• enophthalmos (sunken eye), periorbital ecchymoses

Investigations

• plain films: Waters' view and lateral
• CT: anteroposterior and coronal view of orbits

Treatment

• refrain from coughing, blowing nose
• systemic antibiotics may be indicated
• surgery if fracture >50% orbital floor, diplopia not improving, or enophthalmos >2 mm
• may delay surgery if the diplopia improves

Chemical Burns

• alkali burns have a worse prognosis than acid burns because acids coagulate tissue and inhibit further corneal penetration
• poor prognosis if cornea opaque, likely irreversible stromal damage
• even with a clear cornea initially, alkali burns can progress for weeks (thus, very guarded prognosis)

Treatment

• immediately irrigate at site of accident with water or buffered solution
  ▪ IV drip for at least 20-30 min with eyelids retracted in emergency department
  ▪ swab upper and lower fornices to remove possible particulate matter
• do not attempt to neutralize because the heat produced by the reaction will damage the cornea
• cycloplegic drops to decrease iris spasm (pain) and prevent secondary glaucoma (due to posterior synechiae formation)
• topical antibiotics and patching
• topical steroids (by ophthalmologist) to decrease inflammation, use for <2 wk (in the case of a persistent epithelial defect)
**Surgical Ophthalmology**

- **dacrystorhinostomy (DCR):** excision of bone covering the nasolacrimal sac to restore tear drainage
- **blepharoplasty:** oculoplastic surgical correction of the eyelid by the excision and removal or repositioning of excess skin, fat, and/or the reinforcement of the corresponding muscle and tendon
- **LASIK (laser-assisted in situ keratomileusis):** a microkeratome is used to create a corneal flap followed by laser remodeling of the stroma to correct refractive error
- **trabeculectomy:** creation of a new outflow tract from anterior chamber to under conjunctiva; fibrosis prevented with mitomycin C or 5-FU injection during surgery
- **phacoemulsification (cataract extraction):** the use of ultrasonic waves to break up and aspirate a cataract followed by replacement with an artificial lens implant
- **femtosecond laser-assisted cataract surgery:** uses focused ultrashort pulses (10⁻¹⁵ of a second) to perform photodissection in achieving capsulorrhexis and lens fragmentation
- **vitrectomy:** the use of small gauge trochars to enter the posterior segment and remove vitreous; commonly used to treat vitreous hemorrhage and RD
- **pneumatic retinopexy:** intraocular injection of air or an expandable gas in order to tamponade a retinal break for repair of RD
- **scleral buckle:** a silicone band is secured on the outside of the globe that indents the eye wall, thereby relieving vitreous traction on the retina around any tears/holes and allowing the tears/holes to remain sealed for repair of RD
- **minimally invasive glaucoma surgery (MIGS):** implantation of IOP lowering drainage devices (e.g. iStent) through an ab interno microincisional approach during cataract surgery.

---

**Ocular Drug Toxicity**

**Table 10. Drugs with Ocular Toxicity**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Ocular Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amiodarone</td>
<td>Corneal microdeposits and superficial keratopathy (vortex keratopathy)</td>
</tr>
<tr>
<td></td>
<td>Rare: ischemic optic neuropathy</td>
</tr>
<tr>
<td>Atropine, benztropine</td>
<td>Pupillary dilation (risk of angle closure glaucoma)</td>
</tr>
<tr>
<td>Bisphosphonates (Fosamax®, Actonel®)</td>
<td>Inflammatory eye disease (iritis, scleritis, episcleritis)</td>
</tr>
<tr>
<td>Chloroquine, hydroxychloroquine</td>
<td>Bull’s eye maculopathy</td>
</tr>
<tr>
<td></td>
<td>Vortex keratopathy</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>Anterior subcapsular cataract</td>
</tr>
<tr>
<td>Contraceptive pills</td>
<td>Decreased tolerance to contact lenses</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>Optic neuritis</td>
</tr>
<tr>
<td></td>
<td>Central vein occlusion, benign increase intracranial pressure</td>
</tr>
<tr>
<td>Digitalis</td>
<td>Yellow vision</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Haloperidol (Haldol®)</td>
<td>Oculogyric crises</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Superficial keratopathy</td>
</tr>
<tr>
<td>Interferon</td>
<td>Retinal hemorrhages and cotton wool spots</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Nalidixic acid</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Steroids</td>
<td>Posterior subcapsular cataracts</td>
</tr>
<tr>
<td></td>
<td>Glaucoma</td>
</tr>
<tr>
<td></td>
<td>Papilledema (systemic steroids)</td>
</tr>
<tr>
<td></td>
<td>Increased severity of HSV infections (geographic ulcers)</td>
</tr>
<tr>
<td></td>
<td>Predisposition to fungal infections</td>
</tr>
<tr>
<td>Sulphonamides, NSAIDs</td>
<td>Stevens-Johnson syndrome</td>
</tr>
<tr>
<td>Tamsulosin (Romax®)</td>
<td>Intraoperative Floppy Iris Syndrome, which can complicate cataract surgery</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>Papilledema (associated with pseudotumour cerebri)</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Pigmentary degeneration of retina</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Retinal deposition with macular sparing, peripheral visual field loss</td>
</tr>
<tr>
<td>Vitamin A toxicity</td>
<td>Papilledema</td>
</tr>
<tr>
<td>Vitamin D toxicity</td>
<td>Band keratopathy</td>
</tr>
</tbody>
</table>
Common Medications

TOPICAL OCULAR DIAGNOSTIC DRUGS

**Fluorescein Dye**
- water soluble orange-yellow dye
- green under cobalt blue light (ophthalmoscope or slit-lamp)
- absorbed in areas of epithelial loss (ulcer or abrasion)
- also stains mucus and contact lenses

**Rose Bengal Stain**
- stains devitalized epithelial cells and mucus

Anesthetics
- e.g. proparacaine HCl 0.5%, tetracaine 0.5%
- indications: removal of foreign body and sutures, tonometry, examination of painful cornea
- toxic to corneal epithelium (inhibit mitosis and migration) and can lead to corneal ulceration and scarring with prolonged use, therefore **NEVER** prescribe

Mydriatics
- dilate pupils
- two classes
  - cholinergic blocking (e.g. tropicamide – Mydriacyl®)
    - dilation plus cycloplegia (loss of accommodation) by paralysis of iris sphincter and the ciliary body
    - indications: refraction, ophthalmoscopy, therapy for iritis
  - adrenergic stimulating (e.g. phenylephrine HCl 2.5%)
    - stimulate pupillary dilator muscles, no effect on accommodation
    - usually used with tropicamide for additive effects
    - side effects: HTN, tachycardia, arrhythmias

<table>
<thead>
<tr>
<th>Drugs Des</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide (Mydriacyl®) 0.5%, 1%</td>
<td>4-5 h</td>
</tr>
<tr>
<td>Cyclopentolate HCL 0.5%, 1%</td>
<td>3-6 h</td>
</tr>
<tr>
<td>Homatropine HBr 1%, 2%</td>
<td>3-7 d</td>
</tr>
<tr>
<td>Atropine sulfate 0.5%, 1%</td>
<td>1-2 wk</td>
</tr>
<tr>
<td>Scopolamine HBr 0.25%, 5%</td>
<td>1-2 wk</td>
</tr>
</tbody>
</table>

GLAUCOMA MEDICATIONS

**Table 11. Mydriatic Cycloplegic Drugs and Duration of Action**

<table>
<thead>
<tr>
<th>Drugs Des</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tropicamide (Mydriacyl®) 0.5%, 1%</td>
<td>4-5 h</td>
</tr>
<tr>
<td>Cyclopentolate HCL 0.5%, 1%</td>
<td>3-6 h</td>
</tr>
<tr>
<td>Homatropine HBr 1%, 2%</td>
<td>3-7 d</td>
</tr>
<tr>
<td>Atropine sulfate 0.5%, 1%</td>
<td>1-2 wk</td>
</tr>
<tr>
<td>Scopolamine HBr 0.25%, 5%</td>
<td>1-2 wk</td>
</tr>
</tbody>
</table>

**Table 12. Glaucoma Medications**

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Dose</th>
<th>Effect</th>
<th>Comment/Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>α-Agonist</td>
<td>1 gtt OS/OD bid/tid</td>
<td>↓ aqueous production</td>
<td>1. Non-selective: ↓ aqueous production + ↑ TM outflow</td>
</tr>
<tr>
<td>Non-selective</td>
<td></td>
<td></td>
<td>2. Selective: ↓ aqueous production + ↑ uveoscleral outflow</td>
</tr>
<tr>
<td>+ selective</td>
<td></td>
<td></td>
<td>1. Non-selective: mydriasis, macular edema, tachycardia</td>
</tr>
<tr>
<td>- selective</td>
<td></td>
<td></td>
<td>2. Selective: contact allergy, hypotension in children</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>1 gtt OS/OD qd/bid</td>
<td>↓ aqueous production</td>
<td>Bronchospasm (caution in asthma/COPD)</td>
</tr>
<tr>
<td>Non-selective</td>
<td></td>
<td></td>
<td>1. CHF</td>
</tr>
<tr>
<td>+ selective</td>
<td></td>
<td></td>
<td>2. Bradycardia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Hypotension</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5. Heart block</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6. Impotence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>7. Impotence</td>
</tr>
<tr>
<td>Carbonic Anhydrase Inhibitor</td>
<td>1 gtt OS/OD tid Diamox®: 500 mg PO bid</td>
<td>↓ aqueous production</td>
<td>Must ask about sulfa allergy</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Generally local side effects with topical preparations</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ophthalmic, fatigue, mydriasis, mydriasis, etc.</td>
</tr>
<tr>
<td>Parasympathomimetic</td>
<td>1-2 gtt OS/OD tid/qid</td>
<td>↑ TM outflow</td>
<td>Miosis</td>
</tr>
<tr>
<td>(cholinergic stimulating)</td>
<td></td>
<td></td>
<td>J. night vision</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ GI motility</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑ Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↓ Heart rate</td>
</tr>
<tr>
<td>Prostaglandin Analogues</td>
<td>1 gtt OS/OD qhs</td>
<td>↑ uveoscleral outflow (uveoscleral responsible for 20% of drainage)</td>
<td>Iris colour change</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Periorbital skin pigmentation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lash growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conjunctival hyperemia</td>
</tr>
</tbody>
</table>

**KEY**
- Green: Cholinergics
- Red: Anti-Cholinergics
- White: Anesthetics, Antibiotics, Artificial tears, Steroids
- Yellow: Beta-Blockers
- Blue: Beta-Blocker combinations
- Orange: Carbonic Anhydrase Inhibitors
- Tan: Fluoroquinolones
- Grey: NSAIDs
- Pink: Anti-inflammatories, Steroids

Condensed® = timolol + dorzolamide; Kalacorn® = timolol + latanoprost; Combigan® = timolol + brimonidine; DuxTrav® = timolol + travoprost; gtt = drop, gtts = drops
WET AGE-RELATED MACULAR DEGENERATION MEDICATIONS

VEGF Inhibitors
- block VEGF which prevents ocular angiogenesis and further development of choroidal neovascularization
- administered via intravitreal injections
- pegaptanib (Macugen®) is a selective anti-VEGF targeting VEGF isoform 165 (no longer widely used)
- ranibizumab (Lucentis®) is a non-selective anti-VEGF agent
- aflibercept (Eylea®) is an VEGF "trap" agent that binds VEGF-A and placental growth factor
- bevacizumab (Avastin®) is another non-selective anti-VEGF agent but is only FDA approved for metastatic breast cancer, colorectal cancer, and non-small cell lung cancer; therefore, its widespread ophthalmologic use is off-label

TOPICAL OCULAR THERAPEUTIC DRUGS

NSAIDs
- used for less serious chronic inflammatory conditions
- e.g. ketorolac (Acular®), diclofenac (Voltaren®), nepafenac (Nevanac®) drops

Anti-Histamines
- used to relieve red and itchy eye, often in combination with decongestants
- sodium cromoglycate – stabilizes membranes

Decongestants
- weak adrenergic stimulating drugs (vasoconstrictor)
- e.g. naphazoline, phenylephrine (Isoto Frin®)
- rebound vasodilation with overuse; rarely can precipitate angle closure glaucoma

Antibiotics
- indications: bacterial conjunctivitis, keratitis, or blepharitis
- commonly as topical drops or ointments, may give systemically
- e.g. sulfonamide (sodium sulfacetamide, sulfisoxazole), gentamicin (Garamycin®), erythromycin, tetracycline, bacitracin, polymyxin B, fluoroquinolones (ciprofloxacin [Ciloxan®], ofloxacin [Ocufox®], moxifloxacin [Vigamox®], gatifloxin [Zymar®])

Corticosteroids
- e.g. fluorometholone (FML®), betamethasone, dexamethasone (Maxidex®), prednisolone (Predsol® 0.5%, Pred Forte® 1%), rimexolone (Vexol®), loteprednol etabonate 0.5% (Lotamax®), dexamethasone (Durezol®)
- primary care physicians should avoid prescribing topical corticosteroids due to risk of glaucoma, cataracts, and reactivation of HSV keratitis
- complications
  - potentiates HSV keratitis and fungal keratitis as well as masks symptoms
  - increased IOP more rapidly in steroid responders (within weeks)
  - posterior subcapsular cataract (within months)

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Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles

Acronyms

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>acromioclavicular</td>
</tr>
<tr>
<td>ACL</td>
<td>anterior cruciate ligament</td>
</tr>
<tr>
<td>ABN</td>
<td>anterior interosseous nerve</td>
</tr>
<tr>
<td>AP</td>
<td>anterior posterior</td>
</tr>
<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
</tr>
<tr>
<td>AVN</td>
<td>avascular necrosis</td>
</tr>
<tr>
<td>CA</td>
<td>coracoacromial</td>
</tr>
<tr>
<td>CC</td>
<td>coracoclavicular</td>
</tr>
<tr>
<td>CRPS</td>
<td>complex regional pain syndrome</td>
</tr>
<tr>
<td>DDH</td>
<td>developmental dysplasia of the hip</td>
</tr>
<tr>
<td>DRIJ</td>
<td>distal radioulnar joint</td>
</tr>
<tr>
<td>DVT</td>
<td>deep vein thrombosis</td>
</tr>
<tr>
<td>EdH</td>
<td>ethanol/alcohol</td>
</tr>
<tr>
<td>FAI</td>
<td>femoroacetabular impingement</td>
</tr>
<tr>
<td>FOSH</td>
<td>fall on outstretched hand</td>
</tr>
<tr>
<td>GA</td>
<td>general anesthetic</td>
</tr>
<tr>
<td>HD</td>
<td>heterotopic ossification</td>
</tr>
<tr>
<td>IleD</td>
<td>incision and drainage</td>
</tr>
<tr>
<td>IM</td>
<td>intramedullary</td>
</tr>
<tr>
<td>LCL</td>
<td>lateral collateral ligament</td>
</tr>
<tr>
<td>MCL</td>
<td>medial collateral ligament</td>
</tr>
<tr>
<td>MT</td>
<td>metatarsal</td>
</tr>
<tr>
<td>MTP</td>
<td>metatarsophalangeal</td>
</tr>
<tr>
<td>MVC</td>
<td>motor vehicle collision</td>
</tr>
<tr>
<td>NVS</td>
<td>neurovascular status</td>
</tr>
<tr>
<td>SN</td>
<td>sensitivity</td>
</tr>
<tr>
<td>THA</td>
<td>total hip arthroplasty</td>
</tr>
<tr>
<td>WB</td>
<td>weight bearing</td>
</tr>
<tr>
<td>#</td>
<td>fracture</td>
</tr>
</tbody>
</table>

Basic Anatomy Review

ANTERIOR VIEW

Figure 1. Median, musculocutaneous, and ulnar nerves: innervation of upper limb muscles
Figure 2. (Left) Blood supply to the upper limb, (Right) Axillary and radial nerves: innervation of the upper limb

Table 1. Sensory and Motor Innervation of the Nerves in the Upper and Lower Extremities

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Motor</th>
<th>Sensory</th>
<th>Nerve Roots</th>
</tr>
</thead>
<tbody>
<tr>
<td>Axillary</td>
<td>Deltoid/Teres Minor</td>
<td>Lateral Upper Arm (Sergeant’s Patch)</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Biceps/Brachialis</td>
<td>Lateral Forearm</td>
<td>C5, C6</td>
</tr>
<tr>
<td>Radial</td>
<td>Triceps/Wrist/Thumb/Finger Extensors</td>
<td>Lateral Dorsum of the Hand</td>
<td>C5, C6, C7, C8</td>
</tr>
<tr>
<td>Median</td>
<td>Wrist Flexors and Abdutors</td>
<td>Volar Thumb to Radial half of 4th Digit</td>
<td>C6, C7</td>
</tr>
<tr>
<td>Ulnar</td>
<td>Wrist Flexors and Abdutors</td>
<td>Medial Dorsum and Volar of Hand (Ulnar half of 4th and 5th Digit)</td>
<td>C8, T1</td>
</tr>
<tr>
<td>Tibial</td>
<td>Ankle Plantar Flexion</td>
<td>Sole of Foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td></td>
<td>Knee Flexion</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Great Toe Flexion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Superficial Peroneal</td>
<td>Ankle Eversion</td>
<td>Dorsum of Foot</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Deep Peroneal</td>
<td>Ankle Dorsiflexion and Inversion</td>
<td>1st Web Space</td>
<td>L5, S1</td>
</tr>
<tr>
<td>Sural</td>
<td>Lateral Foot</td>
<td></td>
<td>S1, S2</td>
</tr>
<tr>
<td>Saphenous</td>
<td>Anteromedial Ankle</td>
<td></td>
<td>L3, L4</td>
</tr>
</tbody>
</table>
Fractures – General Principles

Fracture Description

1. Name of Injured Bone

2. Integrity of Skin/Soft Tissue
   - closed: skin/soft tissue over and near fracture is intact
   - open: skin/soft tissue over and near fracture is lacerated or abraded, fracture exposed to outside environment
     - signs: continuous bleeding from puncture site or fat droplets in blood are suggestive of an open fracture
3. Location
- epiphyseal: end of bone, forming part of the adjacent joint
- metaphyseal: the flared portion of the bone at the ends of the shaft
- diaphyseal: the shaft of a long bone (proximal, middle, distal)
- physis: growth plate

4. Orientation/Fracture Pattern
- transverse: fracture line perpendicular to long axis of bone; result of direct high energy force
- oblique: angular fracture line; result of angular or rotational force
- butterfly: fracture site fragment which looks like a butterfly
- segmental: a separate segment of bone bordered by fracture lines; result of high energy force
- spiral: complex, multi-planar fracture line; result of rotational force, low energy
- comminuted/multi-fragmentary: >2 fracture fragments
- intra-articular: fracture line crosses articular cartilage and enters joint
- avulsion: tendon or ligament tears/pulls off bone fragment; often in children, high energy
- compression/impacted: impaction of bone; typical sites are vertebrae or proximal tibia
- torus: a buckle fracture of one cortex, often in children
- greenstick: an incomplete fracture of one cortex, often in children
- pathologic: fracture through bone weakened by disease/tumour

5. Alignment of Fracture Fragments
- nondisplaced: fracture fragments are in anatomic alignment
- displaced: fracture fragments are not in anatomic alignment
- distracted: fracture fragments are separated by a gap (opposite of impacted)
- impacted: fracture fragments are compressed, resulting in shortened bone
- angulated: direction of fracture apex (e.g. varus/valgus)
- translated/shifted: percentage of overlapping bone at fracture site
- rotated: fracture fragment rotated about long axis of bone

Figure 4. Fracture types

Figure 5. Schematic diagram of the long bone

Approach to Fractures

1. Clinical Assessment
- ABCs, primary survey and secondary survey (ATLS protocol)
  - rule out other fractures/injuries
  - rule out open fracture
- AMPLE history (minimum): Allergies, Medications, Past medical history, Last meal, Events surrounding injury
  - mechanism of injury
  - previous significant injury or surgery to affected area
  - consider pathologic fracture with history of only minor trauma
- physical exam: look (deformity, soft tissue integrity); feel (maximal tenderness, NVS-document best possible neurovascular exam, avoid ROM/moving injured area to prevent exacerbation)

2. Analgesia
3. Imaging (see Orthopedic X-Ray Imaging, OR7)
4. Splint Extremity
5. Management: Closed vs. Open Reduction
   1. obtain the reduction (for appropriate IV sedation see Table 27, OR50)
      - closed reduction
        - apply traction in the long axis of the limb
        - reverse the mechanism that produced the fracture
        - reduce with IV sedation and muscle relaxation (fluoroscopy can be used if available)
• indications for open reduction
  ◦ “NO CAST”
  ◦ other indications include
    – failed closed reduction
    – not able to cast or apply traction due to site (e.g. hip fracture)
    – pathologic fractures
    – potential for improved function with ORIF
• ALWAYS re-check and document NVS after reduction and obtain post-reduction x-ray

2. maintain the reduction
• external stabilization: splints, casts, traction, external fixator
• internal stabilization: percutaneous pinning, extramedullary fixation (screws, plates, wires), IM fixation (rods)
• follow-up: evaluate bone healing
3. rehabilitate to regain function and avoid joint stiffness

Fracture Healing

Normal Healing

Weeks 0-3  Hematoma, macrophages surround fracture site
Weeks 3-6  Osteoclasts remove sharp edges, callus forms within hematoma
Weeks 6-12  Bone forms within the callus, bridging fragments
Months 6-12  Cortical gap is bridged by bone
Years 1-2  Normal architecture is achieved through remodelling

Figure 7. Stages of bone healing

Evaluation of Healing: Tests of Union
• clinical: no longer tender to palpation or stressing on physical exam
• x-ray: trabeculae cross fracture site, visible callus bridging site on at least 3 of 4 cortices

General Fracture Complications

Table 2. General Fracture Complications

<table>
<thead>
<tr>
<th>Early</th>
<th>Late</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td></td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Mal-union/ non-union</td>
</tr>
<tr>
<td>Neurological injury</td>
<td>AVN</td>
</tr>
<tr>
<td>Vascular injury</td>
<td>Osteomyelitis</td>
</tr>
<tr>
<td>Infection</td>
<td>HO</td>
</tr>
<tr>
<td>Implant failure</td>
<td>Post-traumatic OA</td>
</tr>
<tr>
<td>Fracture blisters</td>
<td>Joint stiffness/adhesive capsulitis</td>
</tr>
<tr>
<td></td>
<td>CRPS type I/IVSD</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td></td>
</tr>
<tr>
<td>DVT</td>
<td></td>
</tr>
<tr>
<td>PE</td>
<td></td>
</tr>
<tr>
<td>ARDS secondary to fat embolism</td>
<td></td>
</tr>
<tr>
<td>Hämorrhagic shock</td>
<td></td>
</tr>
</tbody>
</table>

Articular Cartilage

Properties
• 2-4 mm layer covering ends of articulating bones, provides nearly frictionless surface
• avascular (nutrition from synovial fluid, aneural, alymphatic
• composed of: collagen (90% is type II; gives tensile strength), water, proteoglycans (gives compressive strength), and chondrocytes

ARTICULAR CARTILAGE DEFECTS

Etiology
• overt trauma, repetitive minor trauma (such as repetitive ankle sprains or patellar maltracking); common sports injury
• degenerative conditions such as early stage OA or osteochondritis dissecans

Indications for Open Reduction

NO CAST
Non-union
Open fracture
Neurovascular Compromise
Displaced intra-Articular fracture
Salter-Harris 3,4,5
PolyTrauma

Figure 6. Heterotopic ossification of femoral diaphysis after femur fracture and IM nailing

Wolff’s Law
Bone remodels itself to over time in response to mechanical load to better withstand loading stressors placed upon it

Heterotopic Ossification
The formation of bone in abnormal locations (e.g. in muscle), secondary to pathology

Avascular Necrosis
Ischemia of bone due to disrupted blood supply; commonly in bones covered by cartilage or with distal to proximal blood supply

Fracture Blister
Formation of vesicles or bullae that occur on edematous skin overlying a fractured bone
Clinical Features
- similar to symptoms of OA (joint line pain with possible effusion, etc.)
- often have predisposing factors, such as ligament injury, malalignment of the joint (varus/valgus), obesity, bone deficiency (AVN, osteochondritis dissecans, ganglion bone cysts), inflammatory arthropathy, and familial osteoarthropathy
- may have symptoms of locking or catching related to the torn/displaced cartilage

Investigations
- x-ray (to rule out bony defects and check alignment)
- MRI
- diagnostic arthroscopy (treatment is often guided by what is seen during arthroscopy)

Table 3. Outerbridge Classification of Chondral Defects

<table>
<thead>
<tr>
<th>Grade</th>
<th>Chondral Damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Softening and swelling of cartilage</td>
</tr>
<tr>
<td>II</td>
<td>Fragmentation and fissuring &lt;1/2’ in diameter</td>
</tr>
<tr>
<td>III</td>
<td>Fragmentation and fissuring &gt;1/2’ in diameter</td>
</tr>
<tr>
<td>IV</td>
<td>Erosion of cartilage down to bone</td>
</tr>
</tbody>
</table>

Treatment
- individualized
  - patient factors (age, skeletal maturity, activity level, etc.)
  - defect factors (Outerbridge Classification, subchondral bone involvement, etc.)
- non-operative
  - rest, NSAIDs, bracing
- operative
  - microfracture, osteochondral grafting (autograft or allograft), autologous chondrocyte implantation

Orthopedic X-Ray Imaging

General Principles
- x-ray 1 joint above and 1 below
- obtain at least 2 orthogonal views ± specialized views

Table 4. Orthopedic X-Ray Imaging

<table>
<thead>
<tr>
<th>Site</th>
<th>Injury</th>
<th>X-Ray Views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shoulder</td>
<td>Anterior dislocation</td>
<td>AP, Axillary ± stress view with 10 lb in hand</td>
</tr>
<tr>
<td></td>
<td>Posterior dislocation</td>
<td>Trans-scapular</td>
</tr>
<tr>
<td></td>
<td>AC Frozen shoulder</td>
<td>Zanca view (10-15 cephalic tilt)</td>
</tr>
<tr>
<td>Arm</td>
<td>Humerus #</td>
<td>AP, Lateral, Trans-scapular, Axillary</td>
</tr>
<tr>
<td>Elbow/Forearm</td>
<td>Supracondylar #</td>
<td>AP, Lateral</td>
</tr>
<tr>
<td></td>
<td>Radial head #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monteggia #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Night stick #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Galeazzi #</td>
<td></td>
</tr>
<tr>
<td>Wrist</td>
<td>Colles’ #</td>
<td>AP, Lateral</td>
</tr>
<tr>
<td></td>
<td>Smith #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scaphoid #</td>
<td>Scaphoid (wrist extension and ulnar deviation x 2 wk)</td>
</tr>
<tr>
<td>Pelvis</td>
<td>Pelvic #</td>
<td>AP pelvis, Inlet and outlet views, Judet views</td>
</tr>
<tr>
<td>Hip</td>
<td>Femoral head/neck #</td>
<td>AP, Lateral, Frog-leg lateral</td>
</tr>
<tr>
<td></td>
<td>Intertrochanteric #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SCFE FAI</td>
<td></td>
</tr>
</tbody>
</table>
Table 4. Orthopedic X-Ray Imaging (continued)

<table>
<thead>
<tr>
<th>Site</th>
<th>Injury</th>
<th>X-Ray Views</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee</td>
<td>Knee dislocation</td>
<td>AP standing, lateral</td>
</tr>
<tr>
<td></td>
<td>Femur/tibia #</td>
<td>Skyline – tangential view with knees flexed at 45° to see patellofemoral joint</td>
</tr>
<tr>
<td></td>
<td>Patella #</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella dislocation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patella femoral syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tibia shaft #</td>
<td></td>
</tr>
<tr>
<td>Ankle</td>
<td>Ankle #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Lateral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mortise view: ankle at 15° of internal rotation</td>
<td></td>
</tr>
<tr>
<td>Foot</td>
<td>Talar #</td>
<td>AP</td>
</tr>
<tr>
<td></td>
<td>Calcanial #</td>
<td>Lateral Harris Axial</td>
</tr>
<tr>
<td>Spine</td>
<td>Compression #</td>
<td>AP spine</td>
</tr>
<tr>
<td></td>
<td>Burst #</td>
<td>AP odontoid</td>
</tr>
<tr>
<td></td>
<td>Cervical spine #</td>
<td>Lateral</td>
</tr>
<tr>
<td></td>
<td>Oblique</td>
<td>Swimmer’s view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lateral flexion/extension view: evaluate subluxation of cervical vertebra</td>
</tr>
</tbody>
</table>

Orthopedic Emergencies

**Trauma Patient Workup**

**Etiology**
- high energy trauma e.g. MVC, fall from height
- may be associated with spinal injuries or life-threatening visceral injuries

**Clinical Features**
- local swelling, tenderness, deformity of the limbs, and instability of the pelvis or spine
- decreased level of consciousness, hypotension/hypovolemia
- consider involvement of EtOH or other substances

**Investigations**
- trauma survey (see Emergency Medicine, ER2, ER15)
- x-rays: lateral cervical spine, AP chest, AP pelvis, AP and lateral of all bones suspected to be injured
- other views of pelvis: AP, inlet, and outlet: Judet views for acetabular fracture (for classification of pelvic fractures see Table 18, OR28)

**Treatment**
- ABCDEs and initiate resuscitation for life threatening injuries
- assess genitourinary injury (rectal exam/vaginal exam mandatory)
- external or internal fixation of all fractures
- DVT prophylaxis

**Complications**
- hemorrhage – life threatening (may produce signs and symptoms of hypovolemic shock)
- fat embolism syndrome (SOB, hypoxemia, petechial rash, thrombocytopenia, and neurological symptoms)
- venous thrombosis – DVT and PE
- bladder/urethral/bowel injury
- neurological damage
- persistent pain/stiffness/limp/weakness in affected extremities
- post-traumatic OA of joints with intra-articular fractures
- sepsis if missed open fracture

**Open Fractures**
- fractured bone and hematoma in communication with the external environment

**Emergency Measures**
- ABCs, primary survey and resuscitation as needed
- removal of obvious foreign material
- irrigate with normal saline if grossly contaminated

33% of patients with open fractures have multiple injuries
• cover wound with sterile dressings
• immediate IV antibiotics
• tetanus toxoid or immunoglobulin as needed
• reduce and splint fracture
• NPO and prepare for OR (blood work, consent, ECG, CXR)
  • operative irrigation and debridement within 6-8 h to decrease risk of infection
  • traumatic wound often left open to drain but vacuum-assisted closure dressing may be used
  • re-examine with repeat irrigation and debridement in 48 h

Table 5. Gustilo Classification of Open Fractures

<table>
<thead>
<tr>
<th>Gustilo Grade</th>
<th>Length of Open Wound</th>
<th>Description</th>
<th>Prophylactic Antibiotic Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&lt;1 cm</td>
<td>Minimal contamination and soft tissue injury Simple or minimally comminuted fracture</td>
<td>First generation cephalosporin (cefazolin) for 3 d If allergy use fluoroquinolone If MRSA positive use vancomycin</td>
</tr>
<tr>
<td>II</td>
<td>1-10 cm</td>
<td>Moderate contamination Moderate soft tissue injury</td>
<td>As per Grade I</td>
</tr>
<tr>
<td>III*</td>
<td>&gt;10 cm</td>
<td>IIIA: Extensive soft tissue injury with adequate ability of soft tissue to cover wound IIIB: Extensive soft tissue injury with periosteal stripping and bone exposure; inadequate soft tissue to cover wound IIIC: Vascular injury/compromise</td>
<td>First generation cephalosporin (cefazolin) for 3 d plus Gram-negative coverage (gentamicin) for at least 3 d For soil contamination, penicillin is added for clostridial coverage</td>
</tr>
</tbody>
</table>

*Any high energy, comminuted fracture, shot gun, farmyard/tail/water contamination, exposure to oral flora, or fracture >8 h old is immediately classified as Grade III

Cauda Equina Syndrome

• see Neurosurgery, NS26

Compartment Syndrome

Definition
• increased interstitial pressure in an anatomical compartment (forearm, calf) where muscle and tissue are bounded by fascia and bone (fibro-osseous compartment) with little room for expansion
• interstitial pressure exceeds capillary perfusion pressure leading to muscle necrosis (in 4-6 h) and eventually nerve necrosis

Etiology
• intracompartmental: fracture (particularly tibial shaft fractures, pediatric supracondylar fractures, and forearm fractures), reperfusion injury, crush injury, ischemia
• extracompartmental: constrictive dressing (circumferential cast, poor positioning during surgery), circumferential burn

![Figure 8. Pathogenesis of compartment syndrome](image)

Clinical Features
• pain out of proportion to injury (typically first symptom)
• pain with active contraction of compartment
• pain with passive stretch (most sensitive)
• swollen, tense compartment
• suspicious history

• 5 Ps: late sign – do not wait for these to develop to make the diagnosis!
Investigations
• usually not necessary as compartment syndrome is a clinical diagnosis
• in children or unconscious patients where clinical exam is unreliable, compartment pressure monitoring with catheter AFTER clinical diagnosis is made (normal = 0 mmHg; elevated ≥30 mmHg or [measured pressure – dBP] ≤30 mmHg)

Treatment
• non-operative
  • remove constrictive dressings (casts, splints), elevate limb at the level of the heart
• operative
  • urgent fasciotomy
  • 48-72 h post-operative: wound closure ± necrotic tissue debridement

Complications
• Volkmann’s ischemic contracture: ischemic necrosis of muscle, followed by secondary fibrosis and finally calcification; especially following supracondylar fracture of humerus
• rhabdomyolysis, renal failure secondary to myoglobinuria

Osteomyelitis

• bone infection with progressive inflammatory destruction

Etiology
• most commonly caused by Staphylococcus aureus
• mechanism of spread: hematogenous (most common) vs. direct-inoculation vs. contiguous focus
• risk factors: recent trauma/surgery, immunocompromised patients, DM, IV drug use, poor vascular supply, peripheral neuropathy

Clinical Features
• symptoms: pain and fever
• on exam: erythema, tenderness, edema common ± abscess/draining sinus tract; impaired function/WB

Diagnosis
• see Medical Imaging, MI24
• workup includes: WBC and diff, ESR, CRP, blood culture, aspirate culture/bone biopsy

Table 6. Treatment of Osteomyelitis

<table>
<thead>
<tr>
<th>Acute Osteomyelitis</th>
<th>Chronic Osteomyelitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV antibiotics 4-6 wk; started empirically and adjusted after obtaining blood and aspirate cultures ± surgery (IBG) for abscess or significant involvement ± hardware removal if present</td>
<td>Surgical debridement Antibiotics: both local (e.g. antibiotic beads) and systemic (IV)</td>
</tr>
</tbody>
</table>

Septic Joint

• joint infection with progressive destruction if left untreated
• risk factors: young/elderly (age >80 yr), RA, prosthetic joint, recent joint surgery, skin infection/ulcer, IV drug use, previous intra-articular corticosteroid injection, immune compromise (cancer, DM, alcoholism)

Etiology
• most commonly caused by Staphylococcus aureus in adults
• consider coagulase-negative Staphylococcus in patients with prior joint replacement
• consider Neisseria gonorrhoeae in sexually active adults and newborns
• most common route of infection is hematogenous

Clinical Features
• inability/refusal to bear weight, localized joint pain, erythema, warmth, swelling, pain on active and passive ROM, ± fever

Investigations
• x-ray (to rule out fracture, tumour, metabolic bone disease), ESR, CRP, WBC, blood cultures
• joint aspirate: cloudy yellow fluid, WBC >50,000 with >90% neutrophils, protein level >4.4 mg/dL, joint glucose level <60% blood glucose level, no crystals, positive Gram stain results
• listen for heart murmur (to reduce suspicion of infective endocarditis, use Duke Criteria)

Rapid progression of signs and symptoms (over hours) necessitates need for serial examinations
Plain Film Findings in a Septic Joint
• Early (0-3 d): usually normal; may show soft-tissue swelling or joint space widening from localized edema
• Late (4-6 d): joint space narrowing and destruction of cartilage

Serial C-reactive protein (CRP) can be used to monitor response to therapy
**Shoulder Dislocation**

- **Treatment**
  - IV antibiotics, empiric therapy (based on age and risk factors), adjust following joint aspirate C&S results
  - non-operative
    - therapeutic joint aspiration, serially if necessary (if early diagnosis and joint superficial)
    - operative
    - arthroscopic/open irrigation and irrigation and drainage ± decompression

**Shoulder**

**Shoulder Dislocation**

- complete separation of the glenohumeral joint; may be anterior or posterior

**Investigations**

- anterior dislocation x-rays (AP, trans-scapular, axillary views)
- posterior dislocation x-rays (AP, trans-scapular, axillary) or CT scan

**Table 7. Anterior and Posterior Shoulder Dislocation**

<table>
<thead>
<tr>
<th></th>
<th>Anterior Shoulder Dislocation (&gt;90%)</th>
<th>Posterior Shoulder Dislocation (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MECHANISM</strong></td>
<td>Abducted arm is externally rotated/hyperextended, or blow to posterior shoulder</td>
<td>Adducted, internally rotated, flexed arm FOOSH</td>
</tr>
<tr>
<td></td>
<td>Involuntary, usually traumatic; voluntary, atraumatic</td>
<td>3 Es (epileptic seizure, EtOH, electrocution)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Blow to anterior shoulder</td>
</tr>
<tr>
<td><strong>CLINICAL FEATURES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Symptoms</strong></td>
<td>Pain, arm slightly abducted and externally rotated with inability to internally rotate</td>
<td>Pain, arm is held in adduction and internal rotation; external rotation is blocked</td>
</tr>
<tr>
<td><strong>Shoulder Exam</strong></td>
<td>“Squared off” shoulder</td>
<td>Anterior shoulder flattening, prominent coracoid, palpable mass posterior to shoulder</td>
</tr>
<tr>
<td></td>
<td>Positive apprehension test: patient looks apprehensive with gentle shoulder abduction and external rotation to 90° since humeral head is pushed anteriorly and recreates feeling of anterior dislocation (see Figure 13)</td>
<td>Positive posterior apprehension (&quot;jerk&quot;) test: with patient supine, flex elbow 90° and adduct, internally rotate the arm while applying a posterior force to the shoulder; patient will &quot;jerk&quot; back with the sensation of subluxation (see Figure 13)</td>
</tr>
<tr>
<td></td>
<td>Positive relocation test: a posteriorly directed force applied during the apprehension test relieves apprehension since anterior subluxation is prevented</td>
<td>Note: the posterior apprehension test is used to test for recurrent posterior instability, NOT for acute injury</td>
</tr>
<tr>
<td></td>
<td>Positive sulcus sign: presence of subacromial indentation with distal traction on humerus indicates inferior shoulder instability (see Figure 13)</td>
<td></td>
</tr>
<tr>
<td><strong>Neurovascular Exam Including</strong></td>
<td>Axillary nerve: sensory patch over deltoid and deltoid contraction</td>
<td>Full neurovascular exam as per anterior shoulder dislocation</td>
</tr>
<tr>
<td></td>
<td>Musculocutaneous nerve: sensory patch on lateral forearm and biceps contraction</td>
<td></td>
</tr>
<tr>
<td><strong>RADIOGRAPHIC FINDINGS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Axillary View</strong></td>
<td>Humeral head is anterior</td>
<td>Humeral head is posterior</td>
</tr>
<tr>
<td><strong>Trans-scapular ‘Y’ View</strong></td>
<td>Humeral head is anterior to the centre of the “Mercedes-Benz” sign</td>
<td>Humeral head is posterior to centre of “Mercedes-Benz” sign</td>
</tr>
<tr>
<td><strong>AP View</strong></td>
<td>Sub-coracoid lie of the humeral head is most common</td>
<td>Partial vacancy of glenoid fossa (vacant glenoid sign) and &gt;6 mm space between anterior glenoid rim and humeral head (positive rim sign), humeral head may resemble a lightbulb due to internal rotation (lightbulb sign)</td>
</tr>
<tr>
<td><strong>Hill-Sachs and Bony Bankart Lesions</strong></td>
<td>± Hill-Sachs lesion: compression fracture of posterior humeral head due to forceful impaction of an anteriorly dislocated humeral head against the glenoid rim (see Figure 12)</td>
<td>± reverse Hill-Sachs lesion (75% of cases): divot in anterior humeral head</td>
</tr>
<tr>
<td></td>
<td>± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum with attached bone fragments from the glenoid rim (see Figure 12)</td>
<td>± reverse bony Bankart lesion: avulsion of the posterior glenoid labrum from the bony glenoid rim</td>
</tr>
</tbody>
</table>
Table 7. Anterior and Posterior Shoulder Dislocation (continued)

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>Anterior Shoulder Dislocation (&gt;90%)</th>
<th>Posterior Shoulder Dislocation (5%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closed reduction with IV sedation and muscle relaxation</td>
<td>Closed reduction with sedation and muscle relaxation</td>
<td>Inferior traction on a flexed elbow with pressure on the back of the humeral head</td>
</tr>
<tr>
<td>Traction-countertraction: assistant stabilizes torso</td>
<td></td>
<td></td>
</tr>
<tr>
<td>with a folded sheet wrapped across the chest while the surgeon applies</td>
<td></td>
<td></td>
</tr>
<tr>
<td>gentle steady traction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stimson: while patient lies prone with arm hanging over table edge, hang</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a 5 lb weight on wrist for 15-20 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hippocratic method: place heel into patient’s axilla</td>
<td></td>
<td></td>
</tr>
<tr>
<td>and apply traction to arm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cunningham’s method: low risk, low pain; if not successful try above</td>
<td></td>
<td></td>
</tr>
<tr>
<td>methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obtain post-reduction x-rays</td>
<td>Obtain post-reduction x-rays</td>
<td></td>
</tr>
<tr>
<td>Check post-reduction NVS</td>
<td>Check post-reduction NVS</td>
<td></td>
</tr>
<tr>
<td>Sling x 3 wk (avoid abduction and external rotation), followed by</td>
<td>Sling in abduction and external rotation x 3 wk, followed by shoulder rehabilitation (dynamic</td>
<td></td>
</tr>
<tr>
<td>shoulder rehabilitation</td>
<td>stabilizer strengthening</td>
<td></td>
</tr>
</tbody>
</table>

Prognosis
- recurrence rate depends on age of first dislocation
  - <20 yr = 65-95%; 20-40 yr = 60-70%; >40 yr = 2-4%

Specific Complications
- rotator cuff or capsular or labral tear (Bankart/SLAP lesion), shoulder stiffness
- injury to axillary nerve/artery, brachial plexus
- recurrent/unreduced dislocation (most common complication)

![Figure 11. Posterior view of anterior dislocation causing Hill-Sachs and Bankart lesions](image1)

Figure 12. Shoulder maneuvers

Rotator Cuff Disease
- rotator cuff consists of 4 muscles that act to stabilize humeral head within the glenoid fossa

Table 8. Rotator Cuff Muscles

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Muscle Attachments</th>
<th>Nerve Supply</th>
<th>Muscle Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal</td>
<td>Distal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraspinatus</td>
<td>Scapula</td>
<td>Greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
</tr>
<tr>
<td>Infraspinatus</td>
<td>Scapula</td>
<td>Greater tuberosity of humerus</td>
<td>Suprascapular nerve</td>
</tr>
<tr>
<td>Teres Minor</td>
<td>Scapula</td>
<td>Greater tuberosity of humerus</td>
<td>Axillary nerve</td>
</tr>
<tr>
<td>Subscapularis</td>
<td>Scapula</td>
<td>Lesser tuberosity of humerus</td>
<td>Subscapular nerve</td>
</tr>
</tbody>
</table>

Factors Causing Shoulder Instability
- Shallow glenoid
- Loose capsule
- Ligamentous laxity

Frequency of Dislocations
- Anterior shoulder > Posterior shoulder
- Posterior hip > Anterior hip

The glenohumeral joint is the most commonly dislocated joint in the body since stability is sacrificed for motion.
SPECTRUM OF DISEASE: IMPINGEMENT, TENDONITIS, MICRO OR MACRO TEARS

Etiology
- outlet/subacromial impingement: “painful arc syndrome”, compression of rotator cuff tendons (primarily supraspinatus) and subacromial bursa between the head of the humerus and the undersurface of acromion, AC joint, and CA ligament
  - leads to bursitis, tendonitis, and if left untreated, can lead to rotator cuff thinning and tear
  - anything that leads to a narrow subacromial space
  - glenohumeral muscle weakness leading to abnormal motion of humeral head
  - scapular muscle weakness leading to abnormal motion of acromion
  - acromial abnormalities such as congenital narrow space or osteophyte formation or Type III acromion morphology

Clinical Features
- insidious onset, but may present as an acute exacerbation of chronic disease, night pain and difficulty sleeping on affected side
- pain worse with active motion (especially overhead); passive movement generally permitted
- weakness and loss of ROM especially between 90°-130° (e.g. trouble with overhead activities)
- tenderness to palpation over greater tuberosity
- rule out bicep tendinosis: Speed and Yergason’s tests; SLAP lesion: O’Brien’s test

Investigations
- x-ray: AP view may show high riding humerus relative to glenoid indicating large tear, evidence of chronic tendonitis
- MRI: coronal/sagittal oblique and axial orientations are useful for assessing full/partial tears and tendinopathy ± arthrogram: geyser sign (injected dye leaks out of joint through rotator cuff tear)
- arthrogram: can assess full thickness tears, difficult to assess partial tears

Treatment
- non-operative
  - physiotherapy, NSAIDs ± steroid injection
  - for mild (“wear”) or moderate (“tear”) cases
- operative
  - indication: severe (“repair”)
    - impingement that is refractory to 2-3 mo physiotherapy and 1-2 corticosteroid injections
    - arthroscopic or open surgical repair (ie. acromioplasty, rotator cuff repair)

Table 9. Rotator Cuff Special Tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Examination</th>
<th>Positive Test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jobe’s Test</td>
<td>Supraspinatus: place the shoulder in 90° of abduction and 30° of forward flexion and internally rotate the arm so that the thumb is pointing toward the floor</td>
<td>Weakness with active resistance suggests a supraspinatus tear</td>
</tr>
<tr>
<td>Lift-off Test</td>
<td>Subscapularis: internally rotate arm so dorsal surface of hand rests on lower back; patient instructed to actively lift hand away from back against examiner resistance (use Belly Press Test if too painful)</td>
<td>Inability to actively lift hand away from back suggests a subscapularis tear</td>
</tr>
<tr>
<td>Posterior-Cuff Test</td>
<td>Infraspinatus and teres minor: arm positioned at patient’s side in 90° of flexion; patient instructed to externally rotate arm against the resistance of the examiner</td>
<td>Weakness with active resistance suggests posterior cuff tear</td>
</tr>
<tr>
<td>Neer’s Test</td>
<td>Rotator cuff impingement: passive shoulder flexion</td>
<td>Pain elicited between 130-170° suggests impingement</td>
</tr>
<tr>
<td>Hawkins-Kennedy Test</td>
<td>Rotator cuff impingement: shoulder flexion to 90° and passive internal rotation</td>
<td>Pain with internal rotation suggests impingement</td>
</tr>
<tr>
<td>Painful Arc Test</td>
<td>Rotator cuff tendinopathy: patient instructed to actively abduct the shoulder</td>
<td>Pain with abduction &gt;90° suggests tendinopathy</td>
</tr>
</tbody>
</table>

Results/Conclusions: Among pain provocation tests, a positive painful arc test had the greatest specificity and sensitivity (SP 81%, SN 71%).

Does this Patient with Shoulder Pain have Rotator Cuff Disease? The Rational Clinical Examination Systematic Review
- Study: 5 studies of sufficient quality including 30-203 shoulders and a prevalence of RCD ranging from 33-81%.

Screening Out Rotator Cuff Tears
- No night pain (SN 87.7%)
- No painful arc (SN 97.5%)
- No impingement signs (SN 97.2%)
- No weakness

Returning to the bedside: Using the history and physical examination to identify rotator cuff tears
- JAMA Geni Soc 2000;48:1633-1637

Rotator Cuff Muscles
- SITS
  - Supraspinatus
  - Infraspinatus
  - Teres minor
  - Subscapularis

Ruling in Rotator Cuff Tears – 98% probability of rotator cuff tear if all 3 of the following are present:
- Supraspinatus weakness
- External rotation weakness
- Positive impingement sign(s)

Diagnosis of rotator cuff tears. Lancet 2001; 357:769-770
Acromioclavicular Joint Pathology

- subluxation or dislocation of AC joint
- 2 main ligaments attach clavicle to scapula: AC and CC ligaments

Mechanism
- fall onto shoulder with adducted arm or direct trauma to point of shoulder

Clinical Features
- pain with adduction of shoulder and/or palpation over AC joint
- palpate step deformity between distal clavicle and acromion (with dislocation)
- limited ROM

Investigations
- x-rays: bilateral AP, Zanca view (10-15° cephalic tilt), axillary

Treatment
- non-operative
  - sling 1-3 wk, ice, analgesia, early ROM and rehabilitation
- operative
  - indication: Rockwood Class IV-VI (III if labourer or high level athlete)
  - number of different approaches involving AC/CC ligament reconstruction or screw/hook plate insertion

Pneumothorax or pulmonary contusion are potential complications of severe AC joint dislocation
**Table 10. Rockwood Classification of Acromioclavicular Joint Separation**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Joint sprain, absence of complete tear of either ligament</td>
<td>Non-operative</td>
</tr>
<tr>
<td>II</td>
<td>Complete tear of AC ligament, incomplete tear of CC ligament, without marked elevation of lateral clavicular head</td>
<td>Non-operative</td>
</tr>
<tr>
<td>III</td>
<td>Complete tear of AC and CC ligaments, &gt;5 mm elevation at AC joint, superior aspect of acromion is below the inferior aspect of the clavicle</td>
<td>Most non-operative, operative if labourer or high level athlete. Will heal with step deformity, although most fully functional in 4-6 mo</td>
</tr>
<tr>
<td>IV/VI</td>
<td>Based on the anatomical structure the displaced clavicle is in proximity with</td>
<td>Operative in most cases</td>
</tr>
</tbody>
</table>

**Clavicle Fracture**

- incidence: proximal (5%), middle (80%), or distal (15%) third of clavicle
- common in children (unites rapidly without complications)

**Mechanism**
- fall on shoulder (87%), direct trauma to clavicle (7%), FOOSH (6%)

**Clinical Features**
- pain and tenting of skin
- arm is clasped to chest to splint shoulder and prevent movement

**Investigations**
- evaluate NVS of entire upper limb
- x-ray: AP, 45° cephalic tilt (superior/inferior displacement), 45° caudal tilt (AP displacement)
- CT: useful for medial physeal fractures and sternoclavicular injury

**Treatment**
- medial and middle third clavicle fractures
  - figure-of-eight sling x 1-2 wk
  - early ROM and strengthening once pain subsides
  - if ends overlap >2 cm consider ORIF
- distal third clavicle fractures
  - undisplaced (with ligaments intact): sling x 1-2 wk
  - displaced (CC ligament injury): ORIF

**Specific Complications** (see General Fracture Complications, OR6)
- cosmetic bump usually only complication
- shoulder stiffness, weakness with repetitive activity
- pneumothorax, brachial plexus injuries, and subclavian vessel (all very rare)

**Frozen Shoulder (Adhesive Capsulitis)**

- disorder characterized by progressive pain and stiffness of the shoulder usually resolving spontaneously after 18 mo

**Mechanism**
- primary adhesive capsulitis
  - idiopathic, usually associated with DM
  - usually resolves spontaneously in 9-18 mo
- secondary adhesive capsulitis
  - due to prolonged immobilization
  - shoulder-hand syndrome: CRPS/RSD characterized by arm and shoulder pain, decreased motion, and diffuse swelling
  - following MI, stroke, shoulder trauma
  - poorer outcomes

**Clinical Features**
- gradual onset (weeks to months) of diffuse shoulder pain with:
  - decreased active AND passive ROM
  - pain worse at night and often prevents sleeping on affected side
  - increased stiffness as pain subsides: continues for 6-12 mo after pain has disappeared

**Investigations**
- x-ray: AP (neutral, internal/external rotation), scapular Y, axillary
  - may be normal, or may show demineralization from disease
**Humerus**

## Proximal Humeral Fracture

### Mechanism
- young: high energy trauma (MVC)
- elderly: FOOSH from standing height in osteoporotic individuals

### Clinical Features
- proximal humeral tenderness, deformity with severe fracture, swelling, painful ROM, bruising extends down arm and chest

### Investigations
- test axillary nerve function (deltoid contraction and skin over deltoid)
- x-rays: AP, trans-scapular, axillary are essential
- CT scan: to evaluate for articular involvement and fracture displacement

### Classification
- Neer classification is based on 4 fracture fragments
- displaced: displacement >1 cm and/or angulation >45°
- the Neer system regards displacement, not the fracture line, as meeting criteria for a ‘part’ in the classification scheme
- ± dislocated/subluxed: humeral head dislocated/subluxed from glenoid

### Treatment
- treat osteoporosis if needed
- non-operative
  - nondisplaced: broad arm sling immobilization, begin ROM within 14 d to prevent stiffness
  - minimally displaced (85% of patients) - closed reduction with sling immobilization x 2 wk, gentle ROM
- operative
  - ORIF (anatomic neck fractures, displaced, associated dislocated glenohumeral joint)
  - hemiarthroplasty may be necessary, especially in elderly

### Specific Complications (see General Fracture Complications, OR6)
- AVN, nerve palsy (45% typically axillary nerve), malunion, post-traumatic arthritis

## Humeral Shaft Fracture

### Mechanism
- high energy: direct blows/MVC (especially young); low energy: FOOSH, twisting injuries, metastases (in elderly)

### Clinical Features
- pain, swelling, weakness ± shortening, motion/crepitus at fracture site
- must test radial nerve function before and after treatment: look for drop wrist, sensory impairment dorsum of hand

### Investigations
- x-ray: AP and lateral radiographs of the humerus including the shoulder and elbow joints

### Treatment
- in general, humeral shaft fractures are treated non-operatively
- non-operative
  - ± reduction; can accept deformity due to compensatory ROM of shoulder
  - hanging cast (weight of arm in cast provides traction across fracture site) with collar and cuff sling immobilization until swelling subsides, then Sarmiento functional brace, followed by ROM
- operative
  - indications: open fracture, neurovascular injury, unacceptable fracture alignment, polytrauma, segmental fracture, pathological fracture, “floating elbow” (simultaneous unstable humeral and forearm fractures), intra-articular
  - ORIF: plating (most common), IM rod insertion, external fixation

---

![Figure 15. Fractures of the proximal humerus](https://via.placeholder.com/150)

**Acceptable Humeral Shaft Deformities for Non-Operative Treatment**
- <20° anterior angulation
- <30° varus angulation
- <3 cm of shortening
Specific Complications (see General Fracture Complications, OR6)
• radial nerve palsy: expect spontaneous recovery in 3-4 mo, otherwise send for EMG
• non-union: most frequently seen in middle 1/3
• decreased ROM
• compartment syndrome

Distal Humeral Fracture

Mechanism
• young: high energy trauma (MVC)
• elderly: FOOSH

Clinical Features
• elbow pain and swelling
• assess brachial artery

Investigations
• x-ray: AP and lateral of humerus and elbow
• CT scan: helpful when suspect shear fracture of capitulum or trochlea

Classification
• supracondylar, distal single column, distal bicolumnar and coronal shear fractures

Treatment
• goal is to restore ROM 30-130° flexion (unsatisfactory outcomes in 25%)
• non-operative
  ▪ cast immobilization (in supination for lateral condyle fracture; pronation for medial condyle fractures)
• operative
  ▪ indications: displaced, supracondylar, bicolumnar
  ▪ closed reduction and percutaneous pinning; ORIF; total elbow arthroplasty (bicolumnar in elderly)

Elbow

Supracondylar Fracture

• subclass of distal humerus fracture: extra-articular, fracture proximal to capitulum and trochlea, usually transverse
• most common in pediatric population (peak age ~7 yr old), rarely seen in adults
• AIN injury commonly associated with extension type

Mechanism
• >96% are extension injuries via FOOSH (e.g. fall off monkey bars); <4% are flexion injuries

Clinical Features
• pain, swelling, point tenderness
• neurovascular injury: assess median and radial nerves, radial artery (check radial pulse)

Investigations
• x-ray: AP, lateral of elbow
  ▪ disruption of anterior humeral line suggests supracondylar fracture

Treatment
• reduction indications: evidence of arterial obstruction, unacceptable angulation, displaced (>50%)
• non-operative
  ▪ nondisplaced: long arm plaster slab in 90° flexion x 3 wk
• operative
  ▪ indications: displaced, vascular injury, open fracture
  ▪ requires percutaneous pinning followed by limb cast with elbow flexed <90°
  ▪ in adults, ORIF is necessary

Specific Complications (see General Fracture Complications, OR6)
• stiffness is most common
• brachial artery injury (kinking can occur if displaced fracture), median or ulnar nerve injury, compartment syndrome (leads to Volkmann’s ischemic contracture), malalignment cubitus varus (distal fragment tilted into varus)

Three Joints at the Elbow
• Humeroradial joint
• Humeroulnar joint
• Radioulnar joint

Figure 16. X-ray of transverse displaced supracondylar fracture of humerus with elbow dislocation

Normal carrying angle of elbow is ~10° of valgus

Terrible Triad
• Radial head fracture
• Coronoid fracture
• Elbow dislocation

Figure 17. X-ray of fat pad sign
Radial Head Fracture

- a common fracture of the upper limb in young adults

Mechanism
- FOOSH with elbow extended and forearm pronated

Clinical Features
- marked local tenderness on palpation over radial head (lateral elbow)
- decreased ROM at elbow, ± mechanical block to forearm pronation and supination
- pain on pronation/supination

Investigations
- x-ray: enlarged anterior fat pad ("sail sign") or the presence of a posterior fat pad indicates effusion which could occur with occult radial head fractures

Table 11. Classification and Treatment of Radial Head Fractures

<table>
<thead>
<tr>
<th>Mason Class</th>
<th>Radiographic Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nondisplaced fracture</td>
<td>Elbow slab or sling x 3-5 d with early ROM</td>
</tr>
<tr>
<td>2</td>
<td>Displaced fracture</td>
<td>ORIF if: angulation &gt; 30°, involves ≥1/3 of the radial head, or if ≥3 mm of joint incongruity exists</td>
</tr>
<tr>
<td>3</td>
<td>Comminuted fracture</td>
<td>Radial head excision ± prosthesis (if ORIF not feasible)</td>
</tr>
<tr>
<td>4</td>
<td>Comminuted fracture with posterior elbow dislocation</td>
<td>Radial head excision ± prosthesis</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
- myositis ossificans – calcification of muscle
- recurrent instability (if MCL injured and radial head excised)

Olecranon Fracture

Mechanism
- direct trauma to posterior aspect of elbow (fall onto the point of the elbow) or FOOSH

Clinical Features
- localized pain, palpable defect
- ± loss of active extension due to avulsion of triceps tendon

Investigations
- x-ray: AP and lateral (require true lateral to determine fracture pattern)

Treatment
- non-operative
  - non-displaced (<2 mm, stable): cast x 3 wk (elbow in 90° flexion) then gentle ROM
- operative
  - displaced: ORIF (plate and screws or tension band wiring) and early ROM if stable

Elbow Dislocation

- third most common joint dislocation after shoulder and patella
- anterior capsule and collateral ligaments disrupted

Mechanism
- elbow hyperextension via FOOSH or valgus/supination stress during elbow flexion
- usually the radius and ulna are dislocated together, or the radius head dislocates and the ulna remains ("Monteggia")
- 80% are posterior/posterolateral, anterior are rare and usually devastating

Clinical Features
- elbow pain, swelling, deformity
- flexion contracture
- ± absent radial or ulnar pulses

Investigations
- x-ray: AP and lateral views

Treatment
- assess NVS before reduction: brachial artery, median and ulnar nerves (can become entrapped during manipulation)
• non-operative
  ▪ closed reduction under conscious sedation (post-reduction x-rays required)
  ▪ Parvin’s method: patient lies prone with arm hanging down; apply gentle traction downwards
    on wrist, as olecranon slips distally, gently lift up the arm at elbow to reduce joint
  ▪ long-arm splint with forearm in neutral rotation and elbow in 90° flexion
  ▪ early ROM (<2 wk)
• operative
  ▪ indications: complex dislocation or persistent instability after closed reduction
  ▪ ORIF

Specific Complications (see General Fracture Complications, OR6)
• stiffness (loss of extension), intra-articular loose body, neurovascular injury (ulnar nerve, median nerve, brachial artery), radial head fracture
• recurrent instability uncommon

Epicondylitis

• lateral epicondylitis = “tennis elbow”, inflammation of the common extensor tendon as it inserts into the lateral epicondyle
• medial epicondylitis = “golfer’s elbow”, inflammation of the common flexor tendon as it inserts into the medial epicondyle

Mechanism
• repeated or sustained contraction of the forearm muscles/chronic overuse

Clinical Features
• point tenderness over humeral epicondyle and/or distal to it
• pain upon resisted wrist extension (lateral epicondylitis) or wrist flexion (medial epicondylitis)
• generally a self-limited condition, but may take 6-18 mo to resolve

Treatment
• non-operative (very good outcomes)
  ▪ rest, ice, NSAIDs
  ▪ use brace/strap
  ▪ physiotherapy, stretching, and strengthening
  ▪ corticosteroid injection
• operative
  ▪ indication: failed 6-12 mo conservative therapy
  ▪ percutaneous or open release of common tendon from epicondyle

Forearm

Radius and Ulna Shaft Fractures

Mechanism
• high energy direct or indirect (MVA, fall from height, sports) trauma
• fractures usually accompanied by displacement due to high force

Clinical Features
• deformity, pain, swelling
• loss of function in hand and forearm

Investigations
• x-ray: AP and lateral of forearm ± oblique of elbow and wrist
• CT if fracture is close to joint

Treatment
• goal is anatomic reduction since imperfect alignment significantly limits forearm pronation and supination
• ORIF with plates and screws; closed reduction with immobilization usually yields poor results for displaced forearm fractures (except in children)

Complications (see General Fracture Complications, OR6)
• soft tissue contracture resulting in limited forearm rotation – surgical release of tissue may be warranted
**Monteggia Fracture**

- more common and better prognosis in the pediatric age group when compared to adults
- fracture of the proximal ulna with radial head dislocation and proximal radioulnar joint injury

**Mechanism**
- direct blow on the posterior aspect of the forearm
- hyperpronation
- fall on the hyperextended elbow

**Clinical Features**
- pain, swelling, decreased rotation of forearm ± palpable lump at the radial head
- ulna angled apex anterior and radial head dislocated anteriorly (rarely the reverse deformity occurs)

**Investigations**
- x-ray: AP, lateral elbow, wrist and forearm

**Treatment**
- adults: ORIF of ulna with indirect radius reduction in 90% of patients (ORIF of radius if unsuccessful)
- splint and early post-operative ROM if elbow completely stable, otherwise immobilization in plaster with elbow flexed for 6 wk
- pediatrics: attempt closed reduction and immobilization in plaster with elbow flexed for Bado Type I-III, surgery for Type IV

**Specific Complications** (see General Fracture Complications, OR6)
- PIN: most common nerve injury; observe for 3 mo as most resolve spontaneously
- radial head instability/redislocation
- radioulnar synostosis

**Nightstick Fracture**

- isolated fracture of ulna without dislocation of radial head

**Mechanism**
- direct blow to forearm (e.g. holding arm up to protect face)

**Treatment**
- non-operative
  - non-displaced
  - below elbow cast (x 10 d) followed by forearm brace (~8 wk)
  - operative
    - displaced
    - ORIF if >50% shaft displacement or >10° angulation

**Galeazzi Fracture**

- fracture of the distal radial shaft with disruption of the DRUJ
- most commonly in the distal 1/3 of radius near junction of metaphysis/diaphysis
- 3x more common than Monteggia fracture

**Mechanism**
- hand FOOSH with axial loading of pronated forearm or direct wrist trauma

**Clinical Features**
- pain, swelling, deformity and point tenderness at fracture site

**Investigations**
- x-ray: AP, lateral elbow, wrist and forearm
  - shortening of distal radius >5 mm relative to the distal ulna
  - widening of the DRUJ space on AP
  - dislocation of radius with respect to ulna on true lateral

**Treatment**
- all cases are operative
  - ORIF of radius; afterwards assess DRUJ stability by balloting distal ulna relative to distal radius
    - if DRUJ is stable and reducible, splint for 10-14 d with early ROM encouraged
    - if DRUJ is unstable, ORIF or percutaneous pinning with long arm cast in supination x 6 wk

---

**Bado Type Classification of Monteggia Fractures**

Based on the direction of displacement of the dislocated radial head, generally the same direction as the apex of the ulnar fracture

- Type I: anterior dislocation of radial head and proximal/middle third ulnar fracture (60%)
- Type II: posterior dislocation of radial head and proximal/middle third ulnar fracture (15%)
- Type III: lateral dislocation of radial head and metaphyseal ulnar fracture (20%)
- Type IV – combined: proximal fracture of the ulna and radius, dislocation of the radial head in any direction (<5%)

---

For all isolated radius fractures assess DRUJ to rule out a Galeazzi fracture
Wrist

Colles’ Fracture

• extra-articular transverse distal radius fracture (~2 cm proximal to the radiocarpal joint) with dorsal displacement ± ulnar styloid fracture
• most common fracture in those >40 yr, especially in women and those with osteoporotic bone

Mechanism
• FOOSH

Clinical Features
• “dinner fork” deformity
• swelling, ecchymoses, tenderness

Investigations
• x-ray: AP and lateral wrist

Treatment
• goal is to restore radial height (13 mm), radial inclination (22°), volar tilt (11°) as well as DRUJ stability and useful forearm rotation
• non-operative
  • closed reduction (think opposite of the deformity)
    • hematoma block (sterile prep and drape, local anesthetic injection directly into fracture site) or conscious sedation
    • closed reduction: 1) traction with extension (exaggerate injury), 2) traction with ulnar deviation, pronation, flexion (of distal fragment – not at wrist)
    • dorsal slab/below elbow cast for 5-6 wk
    • x-ray x 1 wk for 3 wk and at cessation of immobilization to ensure reduction is maintained
  • obtain post-reduction films immediately; repeat reduction if necessary
• operative
  • indication: failed closed reduction, or loss of reduction
  • percutaneous pinning, external fixation or ORIF

Smith’s Fracture

• volar displacement of the distal radius (i.e. reverse Colles’ fracture)

Mechanism
• fall onto the back of the flexed hand

Investigations
• x-ray: AP and lateral wrist

Treatment
• usually unstable and needs ORIF
• if patient is poor operative candidate, may attempt non-operative treatment
  • closed reduction with hematoma block (reduction opposite of Colles’)
  • long-arm cast in supination x 6 wk

Complications of Wrist Fractures

• most common complications are poor grip strength, stiffness, and radial shortening
• distal radius fractures in individuals <40 yr of age are usually highly comminuted and are likely to require ORIF
• 80% have normal function in 6-12 mo

Table 12. Early and Late Complications of Wrist Fractures

<table>
<thead>
<tr>
<th>Early Complication</th>
<th>Late Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficult reduction ± loss of reduction</td>
<td>Malunion, radial shortening</td>
</tr>
<tr>
<td>Compartment syndrome</td>
<td>Painful wrist secondary to ulnar prominence</td>
</tr>
<tr>
<td>Extensor pollicis longus tendon rupture</td>
<td>Frozen shoulder (“shoulder-hand syndrome”)</td>
</tr>
<tr>
<td>Acute carpal tunnel syndrome</td>
<td>Post-traumatic arthritis</td>
</tr>
<tr>
<td>Finger swelling with venous block</td>
<td>Carpal tunnel syndrome</td>
</tr>
<tr>
<td>Complications of a tight cast/splint</td>
<td>CRPS/RSD</td>
</tr>
</tbody>
</table>

Figures:
- Figure 22. Colles’ fracture and associated bony deformity
- Figure 23. Normal wrist angles + wrist angles in Colles’ fracture
- Table 12. Early and Late Complications of Wrist Fractures
- Indications for surgical management of Colles’ fracture
Scaphoid Fracture

Epidemiology
- common in young men; not common in children or in patients beyond middle age
- most common carpal bone injured
- may be associated with other carpal or wrist injuries (e.g. Colles' fracture)

Mechanism
- FOOSH: impact of scaphoid on distal radius, most commonly resulting in a transverse fracture through the waist (65%), distal (10%), or proximal (25%) scaphoid

Clinical Features
- pain with resisted pronation
- tenderness in the anatomical "snuff box", over scaphoid tubercle, and pain with long axis compression into scaphoid
- usually nondisplaced

Investigations
- x-ray: AP, lateral, scaphoid views with wrist extension and ulnar deviation
- ± CT or MRI
- bone scan rarely used
- note: a fracture may not be radiologically evident up to 2 wk after acute injury, so if a patient complains of wrist pain and has anatomical snuff box tenderness but a negative x-ray, treat as if positive for a scaphoid fracture and repeat x-ray 2 wk later to rule out a fracture; if x-ray still negative order CT or MRI

Treatment
- early treatment critical for improving outcomes
- non-operative
  - non-displaced (<1 mm displacement/<15° angulation): long-arm thumb spica cast x 4 wk then short arm cast until radiographic evidence of healing is seen (2-3 mo)
- operative
  - displaced: ORIF with headless/countersink compression screw is the mainstay treatment

Specific Complications (see General Fracture Complications, OR6)
- most common: non-union/mal-union (use bone graft from iliac crest or distal radius with fixation to heal)
- AVN of the proximal fragment
- delayed union (recommend surgical fixation)
- scaphoid nonunion advanced collapse (SNAC) – chronic nonunion leading to advanced collapse and arthritis of wrist

Prognosis
- proximal fifth fracture: AVN rate 100%; proximal third fracture: AVN rate 33%
- waist fractures have healing rates of 80-90%
- distal third fractures have healing rates close to 100%

Hand
- see Plastic Surgery, PL26
**Fractures of the Spine**

- see Neurosurgery, NS32

**Cervical Spine**

**General Principles**
- C1 (atlas): no vertebral body, no spinous process
- C2 (axis): odontoid = dens
- 7 cervical vertebrae; 8 cervical nerve roots
- nerve root exits above vertebra (i.e. C4 nerve root exits above C4 vertebra), C8 nerve root exits below C7 vertebra
- radiculopathy = impingement of nerve root
- myelopathy = impingement of spinal cord

**Special Testing**
- compression test: pressure on head worsens radicular pain
- distraction test: traction on head relieves radicular symptoms
- Valsalva test: Valsalva maneuver increases intrathecal pressure and causes radicular pain

**Table 13. Cervical Radiculopathy/Neuropathy**

<table>
<thead>
<tr>
<th>Root</th>
<th>C5</th>
<th>C6</th>
<th>C7</th>
<th>C8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Deltoid</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Interossei</td>
</tr>
<tr>
<td></td>
<td>Biceps</td>
<td>Brachioradialis</td>
<td>Wrist flexion</td>
<td>Digital flexors</td>
</tr>
<tr>
<td></td>
<td>Wrist extension</td>
<td></td>
<td>Finger extension</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>Axillary nerve (patch over lateral deltoid)</td>
<td>Thumb</td>
<td>Index and middle finger</td>
<td>Ring and little finger</td>
</tr>
<tr>
<td>Reflex</td>
<td>Biceps</td>
<td>Biceps</td>
<td>Triceps</td>
<td>Finger jerk</td>
</tr>
<tr>
<td></td>
<td>Brachioradialis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**X-Rays for C-Spine**
- AP spine: alignment
- AP odontoid: atlantoaxial articulation
- lateral
  - vertebral alignment: posterior vertebral bodies should be aligned (translation >3.5 mm is abnormal)
  - angulation: between adjacent vertebral bodies (>11° is abnormal)
  - disc or facet joint widening
  - anterior soft tissue space (at C3 should be ≤3 mm; at C4 should be ≤8-10 mm)
- oblique: evaluate pedicles and intervertebral foramen
- ± swimmer's view: lateral view with arm abducted 180° to evaluate C7-T1 junction if lateral view is inadequate
- ± lateral flexion/extension view: evaluate subluxation of cervical vertebrae
Differential Diagnosis of C-Spine Pain
- neck muscle strain, cervical spondylosis, cervical stenosis, RA (spondylitis), traumatic injury, whiplash, myofascial pain syndrome

C-SPINE INJURY
- see Neurosurgery, NS33

Thoracolumbar Spine

General Principles
- spinal cord terminates at conus medullaris (L1)
- individual nerve roots exit below pedicle of vertebra (i.e. L4 nerve root exits below L4 pedicle)

Special Tests
- straight leg raise: passive lifting of leg (30-70°) reproduces radicular symptoms of pain radiating down posterior/lateral leg to knee ± into foot
- Lasegue maneuver: dorsiflexion of foot during straight leg raise makes symptoms worse or, if leg is less elevated, dorsiflexion will bring on symptoms
- femoral stretch test: with patient prone, flexing the knee of the affected side and passively extending the hip results in radicular symptoms of unilateral pain in anterior thigh

Table 14. Lumbar Radiculopathy/Neuropathy

<table>
<thead>
<tr>
<th>Root</th>
<th>L4</th>
<th>L5</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor</td>
<td>Quadriceps (knee extension + hip adduction)</td>
<td>Extensor hallucis longus</td>
<td>Peroneus longus + brevis (ankle dorsiflexion)</td>
</tr>
<tr>
<td>Tibialis anterior (ankle inversion + dorsiflexion)</td>
<td>Gluteus medius (hip abduction)</td>
<td>Gastrocnemius + soleus (plantar flexion)</td>
<td></td>
</tr>
<tr>
<td>Sensory</td>
<td>Medial malleolus</td>
<td>1st dorsal webspace and lateral leg</td>
<td>Lateral foot</td>
</tr>
<tr>
<td>Screening Test</td>
<td>Squat and Rise</td>
<td>Heel Walking</td>
<td>Walking on Toes</td>
</tr>
<tr>
<td>Reflex</td>
<td>Knee (patellar)</td>
<td>Medial hamstring*</td>
<td>Ankle (Achilles)</td>
</tr>
<tr>
<td>Test</td>
<td>Femoral stretch</td>
<td>Straight leg raise</td>
<td>Straight leg raise</td>
</tr>
</tbody>
</table>

*Unreliable

Differential Diagnosis of Back Pain
1. mechanical or nerve compression (>90%)
   - degenerative (disc, facet, ligament)
   - peripheral nerve compression (disc herniation)
   - spinal stenosis (congenital, osteophyte, central disc)
   - cauda equina syndrome
2. others (<10%)
   - neoplastic (primary, metastatic, multiple myeloma)
   - infectious (osteomyelitis, TB)
   - metabolic (osteoporosis)
   - traumatic fracture (compression, distraction, translation, rotation)
   - spondyloarthropathies (ankylosing spondylitis)
   - referred (aorta, renal, ureter, pancreas)

DEGENERATIVE DISC DISEASE
- loss of vertebral disc height with age results in
  - bulging and tears of annulus fibrosus
  - change in alignment of facet joints
  - osteophyte formation

Mechanism
- compression over time with age

Clinical Features
- axial back pain without radicular symptoms
- pain worse with axial loading and bending
- negative straight leg raise

ABC'S Approach to the Lateral C-Spine X-Ray
A – Alignment/angulation
B – Bony Deformity
C – Cartilage
S – Soft Tissue

C-Spine X-Ray in Trauma
Must see C7-T1

All trauma patients with suspected C-spine injury require immediate immobilization of C-spine at scene of accident with spine board, C-collar, and sandbags
Investigations
• X-ray, MRI, provocative discography

Treatment
• non-operative
  ▪ staying active with modified activity
  ▪ back strengthening
  ▪ NSAIDs
  ▪ do not treat with opioids; no proven efficacy of spinal traction or manipulation
• operative – rarely indicated
  ▪ decompression ± fusion
  ▪ no difference in outcome between non-operative and surgical management at 2 yr

Table 15. Types of Low Back Pain

<table>
<thead>
<tr>
<th></th>
<th>Mechanical Back Pain</th>
<th>Direct Nerve Root Compression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain Dominance</td>
<td>Back</td>
<td>Leg</td>
</tr>
<tr>
<td>Aggravation</td>
<td>Flexion</td>
<td>Extension, standing, walking</td>
</tr>
<tr>
<td>Onset</td>
<td>Gradual</td>
<td>More sudden</td>
</tr>
<tr>
<td>Duration</td>
<td>Long (weeks, months)</td>
<td>Shorter (days, weeks)</td>
</tr>
<tr>
<td>Treatment</td>
<td>Relief of strain, exercise</td>
<td>Relief of strain, exercise</td>
</tr>
</tbody>
</table>

SPINAL STENOSIS
• narrowing of spinal canal <10 mm
• congenital (idiopathic, osteopetrosis, achondroplasia) or acquired (degenerative, iatrogenic – post spinal surgery, ankylosing spondylitis, Paget’s disease, trauma)

Clinical Features
• ± bilateral back and leg pain
• neurogenic claudication
• ± motor weakness
• normal back flexion; difficulty with back extension (Kemp sign)
• positive Straight leg raise, pain not worse with Valsalva

Investigations
• CT/MRI reveals narrowing of spinal canal, but gold standard = CT myelogram

Treatment
• non-operative
  ▪ vigorous physiotherapy (flexion exercises, stretch/strength exercises), NSAIDs, lumbar epidural steroids
• operative
  ▪ indication: non-operative failure >6 mo
  ▪ decompressive surgery

Table 16. Differentiating Claudication

<table>
<thead>
<tr>
<th></th>
<th>Neurogenic</th>
<th>Vascular</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aggravation</td>
<td>With standing or exercise</td>
<td>Walking set distance</td>
</tr>
<tr>
<td>Alleviation</td>
<td>Change in position (usually flexion, sitting, lying down)</td>
<td>Stop walking</td>
</tr>
<tr>
<td>Time</td>
<td>Relief in ~10 min</td>
<td>Relief in ~2 min</td>
</tr>
<tr>
<td>Character</td>
<td>Neurogenic ± neurological deficit</td>
<td>Muscular cramping</td>
</tr>
</tbody>
</table>
MECHANICAL BACK PAIN
• back pain NOT due to prolapsed disc or any other clearly defined pathology

Clinical Features
• dull backache aggravated by activity and prolonged standing
• morning stiffness
• no neurological signs

Treatment
• symptomatic (analgesics, physiotherapy)
• prognosis: symptoms may resolve in 4-6 wk, others become chronic

LUMBAR DISC HERNIATION
• tear in annulus fibrosus allows protrusion of nucleus pulposus causing either a central, posterolateral, or lateral disc herniation, most commonly at L5-S1 > L4-5 > L3-4
• 3:1 male to female
• only 5% become symptomatic
• usually a history of flexion-type injury

Clinical Features
• back dominant pain (central herniation) or leg dominant pain (lateral herniation)
• tenderness between spinous processes at affected level
• muscle spasm ± loss of normal lumbar lordosis
• neurological disturbance is segmental and varies with level of central herniation
  ▪ motor weakness (L4, L5, S1)
  ▪ diminished reflexes (L4, S1)
  ▪ diminished sensation (L4, L5, S1)
• positive straight leg raise
• positive contralateral SLR
• positive Laségue and Bowstring sign
• cauda equina syndrome (present in 1-10%) – surgical emergency

Investigations
• x-ray, MRI, consider a post-void residual volume to check for urinary retention; post-void >100 mL should heighten suspicion for cauda equina syndrome

Treatment
• non-operative
  ▪ symptomatic
    • extension protocol
    • NSAIDS
• operative
  ▪ indication: progressive neurological deficit, failure of symptoms to resolve within 3 mo or cauda equina syndrome due to central disc herniation
  ▪ surgical discectomy
• prognosis
  • 90% of patients improve in 3 mo with non-operative treatment

SPONDYLOLYSIS
• defect in the pars interarticularis with no movement of the vertebral bodies

Mechanism
trauma: gymnasts, weightlifters, backpackers, loggers, labourers

Clinical Features
activity-related back pain, pain with unilateral extension (Michelis' test)
**Investigations**
- oblique x-ray: “collar” break in the “Scottie dog’s” neck
- bone scan
- CT scan

**Treatment**
- non-operative
  - activity restriction, brace, stretching exercise

**ADULT ISTHMIC SPONDYLOLISTHESIS**
- defect in pars interarticularis causing a forward slip of one vertebra on another usually at L5-S1, less commonly at L4-5

**Mechanism**
- congenital (children), degenerative (adults), traumatic, pathological, teratogenic

**Clinical Features**
- lower back pain radiating to buttocks relieved with sitting
- neurogenic claudication
- L5 radiculopathy
- Meyerding Classification (percentage of slip)

**Investigations**
- x-ray (AP, lateral, obliques flexion-extension views), MRI

**Treatment**
- non-operative
  - activity restriction, bracing, NSAIDS
- operative
  - see Table 17

**Table 17. Classification and Treatment of Spondylolisthesis**

<table>
<thead>
<tr>
<th>Class</th>
<th>Percentage of Slip</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-25%</td>
<td>Symptomatic operative fusion only for intractable pain</td>
</tr>
<tr>
<td>2</td>
<td>25-50</td>
<td>Same as above</td>
</tr>
<tr>
<td>3</td>
<td>50-75</td>
<td>Decompression for spondylolisthesis and spinal fusion</td>
</tr>
<tr>
<td>4</td>
<td>75-100</td>
<td>Same as above</td>
</tr>
<tr>
<td>5</td>
<td>&gt;100</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

**Specific Complications**
- may present as cauda equina syndrome due to roots being stretched over the edge of L5 or sacrum

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**Pelvis**

**Pelvic Fracture**

**Mechanism**
- young: high energy trauma, either direct or by force transmitted longitudinally through the femur
- elderly: fall from standing height, low energy trauma
- lateral compression, vertical shear, or anteroposterior compression fractures

**Clinical Features**
- pain, inability to bear weight
- local swelling, tenderness
- deformity of lower extremity
- pelvic instability

**Investigations**
- x-ray: AP pelvis, inlet and outlet views, Judet views (obturator and iliac oblique for acetabular fracture)
  - 6 cardinal radiographic lines of the acetabulum: ilioischial line, iliopectineal line, tear drop, roof, posterior rim, anterior rim
- CT scan useful for evaluating posterior pelvic injury and acetabular fracture
- assess genitourinary injury (rectal exam, vaginal exam, hematuria, blood at urethral meatus)
  - if involved, the fracture is considered an open fracture

---

Possible Radiological Findings
- Pubic rami fractures: superior/inferior
- Pubic symphysis diastasis: common in AP compression (N=5 mm)
- Sacral fractures: common in lateral compression
- SI joint diastasis: common in AP compression (N=1-4 mm)
- Disrupted anterior column (iliopectineal line) or posterior column (ilioischial line)
- “Teardrop” displacement: acetabular fracture
- Iliac, ischial avulsion fractures
- Displacement of the major fragment: superior (VS), open book (APC), bucket handle (LC)
Classification

Table 18. Tile Classification of Pelvic Fractures

<table>
<thead>
<tr>
<th>Type</th>
<th>Stability</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Rotationally stable</td>
<td>A1: fracture not involving pelvic ring (ex: avulsion or iliac wing fracture)</td>
</tr>
<tr>
<td></td>
<td>Vertically stable</td>
<td>A2: minimally displaced fracture of pelvic ring (e.g. ramus fracture)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>A3: transverse sacral fracture</td>
</tr>
<tr>
<td>B</td>
<td>Rotationally unstable</td>
<td>B1: open book (external rotation)</td>
</tr>
<tr>
<td></td>
<td>Vertically stable</td>
<td>B2: lateral compression – ipsilateral</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B2-1: with anterior ring rotation/displacement through ipsilateral rami</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B2-2: with anterior ring rotation/displacement through non-ipsilateral rami (bucket-handle)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B3: Bilateral</td>
</tr>
<tr>
<td>C</td>
<td>Rotationally unstable</td>
<td>C1: unilateral</td>
</tr>
<tr>
<td></td>
<td>Vertically unstable</td>
<td>C1-1: iliac fracture, C1-2: sacroiliac fracture-dislocation C1-3: sacral fracture</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C2: bilateral with 1 side type B and 1 side type C</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C3: bilateral both sides type C</td>
</tr>
</tbody>
</table>

Treatment

- ABCDEs
- non-operative treatment: protected weight bearing
  - indication: stable fracture
- emergency management
  - IV fluids/blood
  - pelvic binder/sheeting
  - external fixation vs. emergent angiography/embolization
  - ± laparotomy (if FAST/DPL positive)
- operative treatment: ORIF
  - indications:
    - unstable pelvic ring injury
    - disruption of anterior and posterior SI ligament
    - symphysis diastasis >2.5 cm
    - vertical instability of the posterior pelvis
    - open fracture

Complications (see General Fracture Complications, OR6)

- hemorrhage (life-threatening)
- injury to rectum or urogenital structures
- obstetrical difficulties, sexual and voiding dysfunction
- persistent SI joint pain
- post-traumatic arthritis of the hip with acetabular fractures
- high risk of DVT/PE

Hip

Hip Dislocation

- full trauma survey (see Emergency Medicine, Initial Patient Assessment/Management, ER2)
- examine for neurovascular injury PRIOR to open or closed reduction
- reduce hip dislocations ASAP (ideally within 6 h) to decrease risk of AVN of the femoral head
- hip precautions (no extreme hip flexion, adduction, internal or external rotation) for 6 wk post-reduction
- see Hip Dislocation Post-Total Hip Arthroplasty, OR30

ANTERIOR HIP DISLOCATION

- mechanism: posteriorly directed blow to knee with hip widely abducted
- clinical features: shortened, abducted, externally rotated limb
- treatment
  - closed reduction under conscious sedation/GA
  - post-reduction CT to assess joint congruity

POSTERIOR HIP DISLOCATION

- most frequent type of hip dislocation
- mechanism: severe force to knee with hip flexed and adducted
  - e.g. knee into dashboard in MVC
- clinical features: shortened, adducted, internally rotated limb
- treatment

Figure 33. Illustration of the Tile classification of pelvic fractures

Figure 34. Rochester method
closed reduction under conscious sedation/GA only if no associated femoral neck fracture or ipsilateral displacement
• ORIF if unstable, intra-articular fragments or posterior wall fracture
• post-reduction CT to assess joint congruity and fractures
• if reduction is unstable, put in traction x 4-6 wk

CENTRAL HIP FRACTURE DISLOCATION
• traumatic injury where femoral head is pushed medially through acetabulum

COMPLICATIONS FOR ALL HIP DISLOCATIONS
• post-traumatic OA
• AVN of femoral head
• fracture of femoral head, neck, or shaft
• sciatic nerve palsy in 25% (10% permanent)
• HO
• thromboembolism – DVT/PE

Hip Fracture

General Features
• acute onset of hip pain
• unable to weight-bear
• shortened and externally rotated leg
• painful ROM

Table 19. Overview of Hip Fractures

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Definition</th>
<th>Mechanism</th>
<th>Special Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral Neck (Subcapital)</td>
<td>Intracapsular (See Garden Classification, Table 20)</td>
<td>Young: MVC, fall from height Elderly: fall from standing, rotational force</td>
<td>Same as general</td>
<td>X-Ray: AP hip, AP pelvis, cross table lateral hip</td>
<td>Closed reduction under fluoroscopy then dynamic hip screw or IM nail</td>
<td>DVT, non-union, AVN, dislocation</td>
</tr>
<tr>
<td>Intertrochanteric Stable: intact posterosmedial cortex</td>
<td>Extracapsular fracture including the greater and lesser trochanters and transitional bone between the neck and shaft</td>
<td>Same as femoral neck fracture Direct or indirect force transmitted to the intertrochanteric area</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-Ray: AP pelvis, AP/lateral hip</td>
<td>Closed reduction under fluoroscopy then dynamic hip screw or IM nail</td>
<td>DVT, varus displacement of proximal fragment, malrotation, non-union, failure of fixation device</td>
</tr>
<tr>
<td>Unstable: non-intact posterosmedial cortex</td>
<td>Fracture begins at or below the lesser trochanter and involves the proximal femoral shaft</td>
<td>Young: high energy trauma Elderly: osteopenic bone + fall, pathological fracture</td>
<td>Ecchymosis at back of upper thigh</td>
<td>X-Ray: AP pelvis, AP/ lateral hip and femur</td>
<td>Closed/open under fluoroscopy then plate fixation or IM nail</td>
<td>Malalignment, non-union, wound infection</td>
</tr>
<tr>
<td>Subtrochanteric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 20. Garden Classification of Femoral Neck Fractures

<table>
<thead>
<tr>
<th>Type</th>
<th>Displacement</th>
<th>Extent</th>
<th>Alignment</th>
<th>Trabeculae</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>&quot;Incomplete&quot;</td>
<td>Valgus or neutral</td>
<td>Malaligned</td>
<td>Internal fixation to prevent displacement (valgus impacted fracture)</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>Complete</td>
<td>Neutral</td>
<td>Aligned</td>
<td>Internal fixation to prevent displacement</td>
</tr>
<tr>
<td>III</td>
<td>Some</td>
<td>Complete</td>
<td>Varus</td>
<td>Malaligned</td>
<td>Young: ORIF Elderly: hemi-/total hip arthroplasty</td>
</tr>
<tr>
<td>IV</td>
<td>Complete</td>
<td>Complete</td>
<td>Varus</td>
<td>Aligned</td>
<td>Young: ORIF Elderly: hemi-/total hip arthroplasty</td>
</tr>
</tbody>
</table>
Arthritis of the Hip

Etiology
- OA, inflammatory arthritis, post-traumatic arthritis, late effects of congenital hip disorders, or septic arthritis

Clinical Features
- pain (groin, medial thigh) and stiffness aggravated by activity, better with rest in OA
- RA: morning stiffness >1 h, multiple joint swelling, hand nodules
- decreased ROM (internal rotation is lost first)
- crepitus
- effusion
- ± fixed flexion contracture leading to apparent limb shortening (Thomas test)
- ± Trendelenburg sign

Investigations
- x-ray: weight bearing views of affected joint
  - OA: joint space narrowing, subchondral sclerosis, subchondral cysts, osteophytes
  - RA: osteopenia, erosion, joint space narrowing, subchondral cysts, symmetric joint space narrowing
- blood work: ANA, RF

Treatment
- non-operative
  - weight reduction, activity modification, physiotherapy, analgesics, walking aids
- operative
  - indication: advanced disease
  - realign = osteotomy; replace = arthroplasty; fuse = arthrodesis
  - complications with arthroplasty: component loosening, dislocation, HO, thromboembolism, infection, neurovascular injury, limb length discrepancy
  - arthroplasty is standard of care in most patients with hip arthritis

Hip Dislocation Post-Total Hip Arthroplasty

- occurs in 1-4% of primary THA and 10-16% of revision THAs
- risk factors: neurological impairment, post-traumatic arthritis, revision surgery, substance abuse

Mechanism
- THA that is unstable when hip is flexed, adducted and internally rotated, or extended and externally rotated (avoid flexing hip >90° or crossing legs for ~6 wk after surgery)

Investigations
- x-ray: AP pelvis, AP and lateral hip

Treatment
- non-operative
  - closed reduction: external abduction splint to prevent hip adduction (most often)
- operative
  - indication: 2 or more dislocations with evidence of polyethylene wear, malalignment, hardware failure
    - revision THA
    - conversion to hemiarthroplasty with a larger femoral head
    - resection arthroplasty is a last resort

Complications
- sciatic nerve palsy in 25% (10% permanent)
- HO
- infection
Femur

Femoral Diaphysis Fracture

Mechanism
• high energy trauma (MVC, fall from height, gunshot wound)
• in children, can result from low energy trauma (spiral fracture)

Clinical Features
• shortened, externally rotated leg (if fracture displaced)
• inability to weight-bear
• often open injury, always a Gustilo III (see Table 5, OR9)
• Winquist and Hansen classification

Investigations
• x-ray: AP pelvis, AP/lateral hip, femur, knee

Treatment
• stabilize patient
• non-operative (uncommon)
  ▪ indication: non-displaced femoral shaft fractures in co-morbid patients
  ▪ long leg cast
• operative
  ▪ ORIF with anterograde IM nail (most common) or retrograde IM nail, external fixator for unstable patients, open fractures, or highly vascular areas, or plate and screws for open growth plates within 24 h
  ▪ early mobilization and strengthening

Complications
• hemorrhage requiring transfusion
• fat embolism leading to ARDS
• extensive soft tissue damage
• ipsilateral hip dislocation/fracture (2-6%)
• nerve injury

Distal Femoral Fracture

• fractures from articular surface to 5cm above metaphyseal flare

Mechanism
• direct high energy force or axial loading
• three types: extra articular, partial articular, complete articular

Clinical Features
• extreme pain
• knee effusion (hemarthrosis)
• shortened, externally rotated leg if displaced
• neurovascular deficits can occur with displaced fracture

Investigations
• x-ray: AP, lateral, traction views (AP, lateral, oblique,
• CT, angiography if diminished pulses

Treatment
• non-operative (uncommon)
  ▪ indication: non-displaced fracture
  ▪ hinged knee brace
• operative
  ▪ indication: displaced fracture, intra-articular fracture, non-union
  ▪ ORIF or retrograde IM nail if supracondylar and non-comminuted
  ▪ early mobilization and strengthening

Complications (see General Fracture Complications, OR6)
• femoral artery tear
• popliteal artery injury
• nerve injury
• extensive soft tissue injury
• angulation deformities
Knee

Evaluation of Knee

Common Complaints

- general orthopedic history
- also inquire about common knee symptoms
  - locking: mechanical block to extension
  - effusion, muscle spasm after injury, arthritis
  - painful clicking (audible)
  - torn meniscus
  - giving way; instability
  - cruciate ligament or meniscal tear, patellar dislocation

Special Tests of the Knee

- anterior and posterior drawer tests
  - demonstrate ACL and PCL, respectively
  - if able to sublux tibia anteriorly (anterior drawer test), then ACL may be torn
  - if able to sublux tibia posteriorly (posterior drawer test), then PCL may be torn
  - anterior drawer test for ACL: 3.8 positive likelihood ratio, 0.30 negative likelihood ratio

- Lachmann test
  - demonstrates torn ACL
  - hold knee in 10-20° flexion, stabilizing the femur
  - try to sublux tibia anteriorly on femur
  - similar to anterior drawer test, more reliable due to less muscular stabilization
  - for ACL: 25.0 positive likelihood ratio, 0.1 negative likelihood ratio

- Thessaly test
  - demonstrates meniscal tear
  - patient stands flat footed on one leg while the examiner provides his or her hands for balance. The patient then flexes the knee to 20° and rotates the femur on the tibia medially and laterally three times while maintaining the 20° flexion
  - positive for a meniscal tear if the patient experiences medial or lateral joint line discomfort
  - for medial meniscus: 29.67 positive likelihood ratio, 0.11 negative likelihood ratio
  - for lateral meniscus: 23.0 positive likelihood ratio, 0.083 negative likelihood ratio

- posterior sag sign
  - demonstrates torn PCL
  - may give a false positive anterior draw sign
  - flex knees and hips to 90°, hold ankles and knees
  - view from the lateral aspect
  - if one tibia sags posteriorly compared to the other, its PCL is torn

- pivot shift sign
  - demonstrates torn ACL
  - start with the knee in extension
  - internally rotate foot, slowly flex knee while palpating and applying a valgus force
  - normal knee will flex smoothly
  - if incompetent ACL, tibia will sublux anteriorly on femur at start of maneuver. During flexion, the tibia will reduce and externally rotate about the femur (the "pivot")
  - reverse pivot shift (start in flexion, externally rotate, apply valgus and extend knee) suggests torn PCL
  - composite assessment for ACL: 25.0 positive likelihood ratio, 0.04 negative likelihood ratio
  - composite assessment for PCL: 21.0 positive likelihood ratio, 0.05 negative likelihood ratio

- collateral ligament stress test
  - palpate ligament for “opening” of joint space while testing
  - with knee in full extension, apply valgus force to test MCL, apply varus force to test LCL
  - repeat tests with knee in 20° flexion to relax joint capsule
  - opening in 20° flexion due to MCL damage only
  - opening in 20° of flexion and full extension is due to MCL, cruciate, and joint capsule damage

- tests for meniscal tear
  - joint line tenderness
  - palpate one side at a time and watch patient’s eyes
  - for meniscal tear: 0.9 positive likelihood ratio, 1.1 negative likelihood ratio
  - crouch compression test
  - joint line pain when squatting (anterior pain suggests patellofemoral pathology)
• McMurray’s test useful collaborative information
  • with knee in flexion, palpate joint line for painful “pop/click”
  • internally rotate foot, varus stress, and extend knee to test lateral meniscus
  • externally rotate foot, valgus stress, and extend knee to test medial meniscus
  • for meniscal tear: 1.3 positive likelihood ratio, 0.8 negative likelihood ratio
• composite assessment for meniscal tears: 2.7 positive likelihood ratio, 0.4 negative likelihood ratio

X-Rays
• AP standing, lateral
• skyline: tangential view with knees flexed at 45° to see patellofemoral joint
• 3-foot standing view: useful in evaluating leg length and varus/valgus alignment
• Ottawa Knee Rules (see Emergency Medicine, ER16)

Cruciate Ligament Tears

• ACL tear much more common than PCL tear

Table 21. Comparison of ACL and PCL Injuries

<table>
<thead>
<tr>
<th></th>
<th>Anterior Cruciate Ligament</th>
<th>Posterior Cruciate Ligament</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anatomy</strong></td>
<td>From medial wall of lateral femoral condyle to the anteromedial and posterolateral intercondylar eminence of the tibial plateau</td>
<td>Lateral wall of medial femoral condyle to posterior intercondylar eminence of the tibial plateau</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Sudden deceleration Hyperextension and internal rotation of tibia on femur (i.e. “plant and turn”)</td>
<td>Sudden posterior displacement of tibia when knee is flexed or hyperextended (e.g. dashboard MVC injury)</td>
</tr>
<tr>
<td><strong>History</strong></td>
<td>Audible “pop” Immediate swelling Knee “giving way” Inability to continue activity</td>
<td>Audible “pop” Immediate swelling Pain with push off Cannot descend stairs</td>
</tr>
<tr>
<td><strong>Physical</strong></td>
<td>Effusion (hemarthrosis) Posterior lateral joint line tenderness Positive anterior drawer Positive Lachmann Pivot shift Test for MCL, meniscal injuries</td>
<td>Effusion (hemarthrosis) Anteromedial joint line tenderness Positive posterior drawer Reverse pivot shift Other ligamentous, bony injuries</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Stable knee with minimal functional impairment: immobilization 2-4 wk with early ROM and strengthening High demand lifestyle: ligament reconstruction</td>
<td>Unstable knee or young person/high-demand lifestyle: ligament reconstruction</td>
</tr>
</tbody>
</table>

Collateral Ligament Tears

Mechanism
• valgus force to knee = MCL tear
• varus force to knee = LCL tear

Clinical Features
• swelling/effusion
• tenderness above and below joint line medially (MCL) or laterally (LCL)
• joint laxity with varus or valgus force to knee
  • laxity with endpoint suggests partial tear
  • laxity with no endpoint suggests a complete tear
• test for other injuries (e.g. O’Donoghue’s unhappy triad), common peroneal nerve injury

Investigations
• x-ray: AP and lateral; MRI

Treatment
• non-operative
  • partial tear: immobilization x 2-4 wk with early ROM and strengthening
  • complete tear: immobilization at 30° flexion
• operative
  • indication: multiple ligamentous injuries
  • surgical repair of ligaments

O’Donoghue’s Unhappy Triad
• ACL rupture
• MCL rupture
• Meniscal damage (medial and/or lateral)

Partial ligamentous tears are much more painful than complete ligamentous tears
Meniscal Tears

- medial tear much more common than lateral tear

Mechanism
- twisting force on knee when it is partially flexed (e.g. stepping down and turning)
- requires moderate trauma in young person but only mild trauma in elderly due to degeneration

Clinical Features
- immediate pain, difficulty weight-bearing, instability, and clicking
- increased pain with squatting and/or twisting
- effusion (hemarthrosis) with insidious onset (24-48 h after injury)
- joint line tenderness medially or laterally
- locking of knee (if portion of meniscus mechanically obstructing extension)

Investigations
- MRI, arthroscopy

Treatment
- non-operative
  - indication: not locked
  - ROM and strengthening (NSAIDs)
- operative
  - indication: locked or failed non-operative treatment
  - arthroscopic repair/partial meniscectomy

Quadriceps/Patellar Tendon Rupture

Mechanism
- sudden forceful contraction of quadriceps during an attempt to stop
- more common in obese patients and those with pre-existing degenerative changes in tendon
  - DM, SLE, RA, steroid use, renal failure on dialysis

Clinical Features
- inability to extend knee or weight-bear
- possible audible "pop"
- patella in lower or higher position with palpable gap above or below patella respectively
- may have an effusion

Investigations
- ask patient to straight leg raise (unable with complete rupture)
- knee x-ray to rule out patellar fracture, MRI to distinguish between complete and partial tears
- lateral view: patella alta with patella tendon rupture, patella baja (infra) with quadriceps tendon rupture

Treatment
- non-operative
  - indication: incomplete tears with preserved extension of knee
  - immobilization in brace
- operative
  - indication: complete ruptures with loss of extensor mechanism
  - early surgical repair: better outcomes compared with delayed repair (>6 wk post injury)
  - delayed repair complicated by quadriceps contracture, patella migration, and adhesions

Dislocated Knee

Mechanism
- high energy trauma
- by definition, caused by tears of multiple ligaments

Clinical Features
- classified by relation of tibia with respect to femur
  - anterior, posterior, lateral, medial, rotary
- knee instability
- effusion
- pain
- ischemic limb
- Schenck classification
Investigations
- x-ray: AP, lateral, skyline
- associated radiographic findings include tibial plateau fracture dislocations, proximal fibular fractures, and avulsion of fibular head
- ankle brachial index (abnormal if <0.9)
- arteriogram or CT angiogram if abnormal vascular exam (such as abnormal pedal pulses)

Treatment
- urgent closed reduction
- complicated by interposed soft tissue
- assessment of peroneal nerve, tibial artery, and ligamentous injuries
- emergent operative repair if vascular injury, open fracture or dislocation, non-reducible dislocation, compartment syndrome
- knee immobilization x 6-8 wk

Specific Complications
- high incidence of associated injuries
- popliteal artery tear
- peroneal nerve injury
- capsular tear
- chronic: instability, stiffness, post-traumatic arthritis

Patella

Patellar Fracture

Mechanism
- direct blow to the patella: fall, MVC (dashboard)
- indirect trauma by sudden flexion of knee against contracted quadriceps

Clinical Features
- marked tenderness
- inability to extend knee or straight leg raise
- proximal displacement of patella
- patellar deformity
- ± effusion/hemarthrosis

Investigations
- x-rays: AP, lateral, skyline
- do not confuse with bipartite patella: congenitally unfused ossification centres with smooth margins on x-ray at superolateral corner

Treatment
- non-operative
  - indication: non-displaced (step-off <2-3 mm and fracture gap <1-4 mm)
    - straight leg immobilization 1-4 wk with hinged knee brace, weight bearing as tolerated
    - progress in flexion after 2-3 wk
    - physiotherapy: quadriceps strengthening when pain has subsided
- operative
  - indication: displaced (>2mm), comminuted, disrupted extensor mechanism
  - ORIF; if comminuted may require partial/complete patellectomy
  - goal: restore extensor mechanism with maximal articular congruency

Patellar Dislocation

Mechanism
- usually a non-contact twisting injury
- lateral displacement of patella after contraction of quadriceps at the start of knee flexion in an almost straight knee joint
- direct blow, e.g. knee/helmet to knee collision

Risk Factors
- young, female
- obesity
- high-riding patella (patella alta)
- knock-knees (genu valgus)
- Q-angle (quadriceps angle) ≥20°
- shallow intercondylar groove
- weak vastus medialis
- tight lateral retinaculum
- ligamentous laxity (Ehlers-Danlos)

Complications
- Symptomatic wiring
- Loss of reduction
- Osteonecrosis (proximal fragment)
- Hardware failure
- Knee stiffness
- Nonunion
- Infection

Figure 43. Types of patellar fractures

Figure 44. Q-angle
The angle between a vertical line through the patella and tibial tuberosity and a line from the ASIS to the middle patella; the larger the angle the greater the amount of lateral force on the knee (normal <20°)
**Clinical Features**
- knee catches or gives way with walking
- severe pain, tenderness anteromedially from rupture of capsule
- weak knee extension or inability to extend leg unless patella reduced
- positive patellar apprehension test
  - passive lateral translation results in guarding and patient apprehension
- often recurrent, self-reducing
- concomitant MCL injury
- increased Q-angle
- J-sign

**Investigations**
- x-rays: AP, lateral, skyline view of patella
  - check for fracture of medial patella (most common) and lateral femoral condyle

**Treatment**
- non-operative first
  - NSAIDs, activity modification, and physical therapy
  - short-term immobilization for comfort then 6 wk controlled motion
  - progressive weight bearing and isometric quadriceps strengthening
- operative
  - indication: if recurrent or if loose bodies present
  - surgical tightening of medial capsule and release of lateral retinaculum, possible tibial tuberosity transfer, or proximal tibial osteotomy

**Patellofemoral Syndrome (Chondromalacia Patellae)**
- syndrome of anterior knee pain associated with idiopathic articular changes of patella

**Risk Factors**
- malalignment causing patellar maltracking (Q angle ≥20°, genu valgus)
- post-treatment
- deformity of patella or femoral groove
- recurrent patellar dislocation, ligamentous laxity
- excessive knee strain (athletes)

**Mechanism**
- softening, erosion and fragmentation of articular cartilage, predominantly medial aspect of patella
- commonly seen in active young females

**Clinical Features**
- deep, aching anterior knee pain
  - exacerbated by prolonged sitting (theatre sign), strenuous athletic activities, stair climbing, squatting or kneeling
- insidious onset and vague in nature
- sensation of instability, pseudolocking
- pain with extension against resistance through terminal 30-40°
- pain with compression of patella with knee ROM or resisted knee extension
- swelling rare, minimal if present
- palpable crepitus

**Investigations**
- x-ray: AP, lateral, skyline – may find chondrosis, lateral patellar tilt, patella alta/baja, or shallow sulcus
- CT-scan
- MRI – best to assess articular cartilage

**Treatment**
- non-operative
  - continue non-impact activities; rest and rehabilitation
  - NSAIDs
  - physiotherapy: vastus medialis and core strengthening
- operative
  - indication: failed non-operative treatment
  - tibial tubercle elevation
  - arthroscopic shaving/debridement
  - lateral release of retinaculum
Tibia

Tibial Plateau Fracture

Mechanism
• varus/valgus load ± axial loading (e.g. fall from height)
• femoral condyles driven into proximal tibia
• can result from minor trauma in osteoporotics

Clinical Features
• frequency: lateral > bicondylar > medial
• medial fractures require higher energy – often have concomitant vascular injuries
• knee effusion
• inability to bear weight
• swelling
• associated with compartment syndrome, ACL injury and meniscal tears
• Schatzker classification

Investigations
• x-ray: AP, lateral, oblique
• CT: pre-operative planning, identify articular depression and comminution
• ABI if any differences in pulses between extremities

Treatment

<table>
<thead>
<tr>
<th>Approach #1 (based on amount of depression seen on x-ray)</th>
<th>Non-operative indication (if depression on x-ray is &lt;3 mm): straight leg immobilization x 4-6 wk with progressive ROM weight bearing ORIF often requiring bone grafting to elevate depressed fragment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approach #2 (based on varus/valgus instability)</td>
<td>Non-operative indication (if minimal varus/valgus instability (&lt;15°)): straight leg immobilization x 4-6 wk with progressive ROM weight bearing Operative indication (if significant varus/valgus instability (&gt;15°)): ORIF often requiring bone grafting to elevate depressed fragment</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
• ligamentous injuries
• meniscal lesions
• AVN
• infection
• OA

Tibial Shaft Fracture

• most common long bone and open fracture

Mechanism
• low energy pattern: torsional injury
• high energy: including MVC, falls, sporting injuries

Clinical Features
• pain, inability to bear weight
• open vs. closed
• amount of displacement
• NVS

Investigations
• x-ray: AP, lateral, skyline
• full length, plus knee and ankle

Treatment

<table>
<thead>
<tr>
<th>Approach</th>
<th>Non-operative indication</th>
<th>Operative indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>non-operative</td>
<td>closed and minimally displaced or adequate closed reduction</td>
<td>ORIF with reamed IM nail, plate and screws, or external fixator</td>
</tr>
<tr>
<td></td>
<td>long leg cast x 8-12 wk, functional brace after</td>
<td>if open: antibiotics, I&amp;D, external fixation or IM nail and vascularized coverage of soft tissue defects (often heal poorly)</td>
</tr>
</tbody>
</table>

Specific Complications (see General Fracture Complications, OR6)
• high incidence of neurovascular injury and compartment syndrome
• poor soft tissue coverage (critical to outcome)

Schatzker Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Involvement of lateral plateau split fracture</td>
</tr>
<tr>
<td>II</td>
<td>Lateral split-depressed fracture</td>
</tr>
<tr>
<td>III</td>
<td>Involvement of lateral plateau: pure depression fracture</td>
</tr>
<tr>
<td>IV</td>
<td>Medial plateau fracture</td>
</tr>
<tr>
<td>V</td>
<td>Bicondylar plateau fracture</td>
</tr>
<tr>
<td>VI</td>
<td>Bicondylar with metaphyseal/diaphyseal involvement</td>
</tr>
</tbody>
</table>

Low Molecular Weight Heparin for Prevention of Venous Thromboembolism in Patients with Lower-Leg Immobilization

Cochrane DB Syst Rev 2014;4:CD006681

Purpose: To evaluate the effectiveness of LMWH as VTE prophylaxis in patients with lower-leg immobilization in an ambulant setting.

Selection Criteria: RCTs and CCTs comparing LMWH to no prophylaxis or placebo in patients immobilized with a plaster cast or brace.

Results/Conclusions: 6 RCTs, 1,490 patients. Incidence of VTE was 4.3-40% in patients immobilized for >1wk without thromboprophylaxis or with placebo. With daily LMWH subcutaneous injections, incidence was 0-37% (OR 0.49, 95% CI 0.34-0.72). There were no reports of heparin-induced thrombocytopenia. The use of LMWH in outpatients with lower-leg immobilization significantly reduces the number of VTE events.
Ankle

Evaluation of Ankle and Foot Complaints

Special Tests
• anterior drawer: examiner attempts to displace the foot anteriorly against a fixed tibia
• talar tilt: foot is stressed in inversion and angle of talar rotation is evaluated by x-ray

X-Ray
• AP, lateral
• mortise view: ankle at 15° of internal rotation
  • gives true view of ankle joint
  • joint space should be symmetric with no talar tilt
• Ottawa Ankle Rules should guide x-ray use (see Emergency Medicine, ER17); nearly 100% sensitivity
• ± CT to better characterize fractures

Ankle Fracture

Mechanism
• pattern of fracture depends on the position of the ankle when trauma occurs
• generally involves
  • ipsilateral ligamentous tears or transverse bony avulsion
  • contralateral shear fractures (oblique or spiral)
• classification systems
  • Danis-Weber
  • Lauge-Hansen: based on foot’s position and motion relative to leg

Danis-Weber Classification
• based on level of fibular fracture relative to syndesmosis
• Type A (infra-syndesmotic)
  • pure inversion injury
  • avulsion of lateral malleolus below plafond or torn calcaneofibular ligament
  • ± shear fracture of medial malleolus
• Type B (trans-syndesmotic)
  • external rotation and eversion (most common)
  • ± avulsion of medial malleolus or rupture of deltoid ligament
  • spiral fracture of lateral malleolus starting at plafond
• Type C (supra-syndesmotic)
  • pure external rotation
  • avulsion of medial malleolus or torn deltoid ligament
  • ± posterior malleolus avulsion with posterior tibio-fibular ligament
  • fibular fracture is above plafond (called Maisonneuve fracture if at proximal fibula)
  • frequently tears syndesmosis

Treatment
• non-operative
  • indication: non-displaced, no history of dislocation, usually lateral sided injury only
  • below knee cast, NWB
• operative
  • indications
    • any fracture-dislocation: restore vascularity, minimize articular injury, reduce pain and skin pressure
    • most of type B, and all of type C
    • trimalleolar (medial, posterior, lateral) fractures
    • talar tilt >10°
    • medial clear space on x-ray greater than superior clear space
    • open fracture/open joint injury
  • ORIF

Complications
• high incidence of post-traumatic arthritis
• wrinkle test: skin shows wrinkles, to determine if soft tissue swelling has resolved to an extent to reduce complications

Ottawa Ankle Rules (see Emergency Medicine, ER17)
X-rays are only required if:
Pain in the malleolar zone AND bony tenderness over the posterior aspect of the medial or lateral malleolus OR inability to weight bear both immediately after injury and in the ER

Figure 46. Ring principle of the ankle and Danis-Weber classification

Legend
1. Posterior malleolus
2. Medial malleolus
3. Deltoid ligament
4. Syndesmosis
5. Lateral malleolus
6. Calcaneofibular ligament
Ligamentous Injuries

• see Figure 48 for ankle ligaments

Medial Ligament Complex (deltoid ligament)
• eversion injury
• usually avulses medial or posterior malleolus and strains syndesmosis

Lateral Ligament Complex (Anterior Talofibular, Calcaneofibular, Posterior Talofibular)
• inversion injury, >90% of all ankle sprains
• ATF most commonly and severely injured if ankle is plantar flexed
• swelling and tenderness anterior to lateral malleolus
• ++ ecchymoses
• positive ankle anterior drawer
• may have significant medial talar tilt on inversion stress x-ray

Treatment
• non-operative
  ▪ microscopic tear (Grade I)
    ▪ rest, ice, compression, elevation (RICE)
  ▪ macroscopic tear (Grade II)
    ▪ strap ankle in dorsiflexion and eversion x 4-6 wk
    ▪ physiotherapy: strengthening and proprioceptive retraining
  ▪ complete tear (Grade III)
    ▪ below knee walking cast x 4-6 wk
    ▪ physiotherapy: strengthening and proprioceptive retraining
    ▪ surgical intervention may be required if chronic symptomatic instability develops

Foot

Talar Fracture

Mechanism
• axial loading or hyperdorsiflexion (MVC, fall from height)
• 60% of talus covered by articular cartilage
• talar neck is most common fracture of talus (50%)
• tenuous blood supply runs distal to proximal along talar neck
  ▪ high risk of AVN with displaced fractures

Investigations
• x-ray: AP, lateral, Canale view
• CT to better characterize fracture
• MRI can clearly define extent of AVN

Treatment
• non-operative
  ▪ indication: non-displaced
    ▪ NWB below knee cast x 6 weeks
  ▪ operative
    ▪ indication: displaced (Hawkin’s Classification)
      ▪ ORIF (high rate of nonunion, AVN)
    ▪ neck fracture: Pin (nondisplaced) or ORIF

Calcaneal Fracture

• most common tarsal fracture

Mechanism
• high energy, axial loading: fall from height onto heels
• 10% of fractures associated with compression fractures of thoracic or lumbar spine (rule out spine injury)
• 75% intra-articular and 10% are bilateral
Clinical Features
• marked swelling, bruising on heel/sole
• wider, shortened, flatter heel when viewed from behind
• varus heel

Investigations
• x-rays: AP, lateral, oblique (Broden’s view) Harris axial
• loss of Bohler’s angle
• CT: gold-standard, assess intra-articular extension

Treatment
• closed vs. open reduction is controversial
• NWB cast x 3 mo with early ROM and strengthening

Achilles Tendonitis
Mechanism
• chronic inflammation from activity or poor-fitting footwear
• may also develop heel bumps (retrocalcaneobursitis or Haglund deformity)

Clinical Features
• pain, stiffness, and crepitus with ROM
• thickened tendon, palpable bump

Investigations
• x-ray: lateral, evaluate bone spur and calcification; U/S, MRI (to assess degenerative change)

Treatment
• non-operative
  • rest, NSAIDs, shoe wear modification
  • heel sleeves and pads are mainstay of non-operative treatment
  • gentle gastrocnemius-soleus stretching, eccentric training with physical therapy, deep tissue calf massage
  • orthotics, open back shoes
  • shockwave therapy in chronic tendinitis
  • DO NOT inject steroids (risk of tendon rupture)

Achilles Tendon Rupture
Mechanism
• loading activity, stop-and-go sports (e.g. squash, tennis, basketball)
• secondary to chronic tendinitis, steroid injection

Clinical Features
• audible pop, sudden pain with push off movement
• sensation of being kicked in heel when trying to plantar flex
• palpable gap
• apprehensive toe off when walking
• weak plantar flexion strength
• Thompson test: with patient prone, plantar flexion when calf is squeezed by examiner
  • no passive plantar flexion is positive test = ruptured tendon

Investigations
• x-ray (to rule out other pathology), U/S or MRI (for partial vs complete ruptures)

Treatment
• non-operative
  • indication: low demand or elderly
  • cast foot in plantar flexion (to relax tendon) x 8-12 wk
• operative
  • indication: high demand
  • surgical repair, then cast as above x 6-8 wk

Complications of Achilles Tendon Rupture
• Infection
• Sural nerve injury
• Re-rupture: surgical repair decreases likelihood of re-rupture compared to non-operative management

Haglund Deformity: an enlargement of the posterior-superior tuberosity of the calcaneus

The most common site of Achilles tendon rupture is 2-6 cm from its insertion where the blood supply is the poorest
Plantar Fasciitis (Heel Spur Syndrome)

- Inflammation of plantar aponeurosis at calcaneal origin
- Common in athletes (especially runners, dancers)
- Also associated with obesity, DM, seronegative and seropositive arthritis

Mechanism
- Repetitive strain injury causing microtears and inflammation of plantar fascia
- Common in athletes (especially runners, dancers)
- Also associated with obesity, DM, seronegative and seropositive arthritis

Clinical Features
- Insidious onset of heel pain, pain when getting out of bed and stiffness
- Intense pain when walking from rest that subsides as patient continues to walk, worse at end of day with prolonged standing
- Swelling, tenderness over sole
- Greatest at medial calcaneal tubercle and 1-2 cm distal along plantar fascia
- Pain with toe dorsiflexion (stretches fascia)

Investigations
- Plain radiographs to rule out fractures
- Often see bony exostoses (heel spurs) at insertion of fascia into medial calcaneal tubercle
- Spur is secondary to inflammation, not the cause of pain

Treatment
- Non-operative
  - Pain control and stretching programs are first line
  - Rest, ice, NSAIDs, steroid injection
  - Physiotherapy: Achilles tendon and plantar fascia stretching, extracorporeal shockwave therapy
  - Orthotics with heel cup – to counteract pronation and disperse heel strike forces
- Operative
  - Indication: failed non-operative treatment
  - Endoscopic surgical release of fascia
  - Spur removal is not required

Bunions (Hallux Valgus)

- Bony deformity characterized by medial displacement of first metatarsal and lateral deviation of hallux

Mechanism
- Valgus alignment on 1st MTP (hallux valgus) causes eccentric pull of extensor and intrinsic muscles
- Many associated deformities in foot from altered mechanics
- Reactive exostosis forms with thickening of the skin creating a bunion
- Most often associated with poor-fitting footwear (high heel and narrow toe box)
- Can be hereditary (70% have family history)
- 10x more frequent in women

Clinical Features
- Painful bursa over medial eminence of 1st MT head
- Pronation (rotation inward) of great toe
- Numbness over medial aspect of great toe

Investigations
- X-ray: standing AP/lateral/sesamoid view, NWB oblique

Treatment
- Indications: painful corn or bunion, overriding 2nd toe
- Non-operative (first line)
  - Properly fitted shoes (low heel) and toe spacer
- Operative: goal is to restore normal anatomy, not cosmetic reasons alone
  - Osteotomy with realignment of 1st MTP joint (Chevron Procedure)
  - Arthrodesis
Metatarsal Fracture

- as with the hand, 1st, 4th, 5th MT are relatively mobile, while the 2nd and 3rd are fixed
- use Ottawa Foot Rules to determine need for x-ray

<table>
<thead>
<tr>
<th>Fracture Type</th>
<th>Mechanism</th>
<th>Clinical</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avulsion of Base of 5th MT</td>
<td>Sudden inversion followed by contraction of peroneus brevis</td>
<td>Tender base of 5th MT</td>
<td>Requires ORIF if displaced</td>
</tr>
<tr>
<td>Midshaft 5th MT (Jones Fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 5th MT</td>
<td>*NWB BK cast x 6 wk ORIF if athlete</td>
</tr>
<tr>
<td>Shaft 2nd, 3rd MT (March Fracture)</td>
<td>Stress injury</td>
<td>Painful shaft of 2nd or 3rd MT</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>1st MT</td>
<td>Trauma</td>
<td>Painful 1st MT</td>
<td>ORIF if displaced otherwise</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>*NWB BK cast x 3 wk then walking cast x 2 wk</td>
</tr>
</tbody>
</table>

Tarso-MT Fracture – Dislocation (Lisfranc Fracture) | Fall onto plantar flexed foot or direct crush injury | Shortened forefoot prominent base | ORIF |

*NWB BK = Non weight bearing, below knee

Pediatric Orthopedics

Fractures in Children

- type of fracture
  - thicker, more active periosteum results in pediatric specific fractures: greenstick (one cortex), torus (i.e. ‘buckle’, impacted cortex) and plastic (bowing)
  - distal radius fracture most common in children (phalanges second), the majority are treated with closed reduction and casting
  - adults fracture through both cortices
- epiphyseal growth plate
  - weaker part of bone, susceptible to fractures
  - plate often mistaken for fracture on x-ray and vice versa (x-ray opposite limb for comparison), especially in elbow
  - tensile strength of bone < ligaments in children, therefore clinician must be confident that fracture and/or growth plate injury have been ruled out before diagnosing a sprain
  - intra-articular fractures have worse consequences in children because they usually involve the growth plate
- anatomic reduction
  - gold standard with adults
  - may cause limb length discrepancy in children (overgrowth)
  - accept greater angular deformity in children (remodelling minimizes deformity)
- time to heal
  - shorter in children
- always be aware of the possibility of child abuse
  - make sure stated mechanism compatible with injury
  - high index of suspicion with fractures in non-ambulating children (<1 yr); look for other signs, including x-ray evidence of healing fractures at different sites and different stages of healing

Stress Fractures

Mechanism
- insufficiency fracture
  - stress applied to a weak or structurally deficient bone
- fatigue fracture
  - repetitive, excessive force applied to normal bone
- most common in adolescent athletes
- tibia is most common site

Diagnosis
- localized pain and tenderness over the involved bone
- plain films may not show fracture for 2 wk
- bone scan positive in 12-15 d

Treatment
- rest from strenuous activities to allow remodelling (can take several months)
Evaluation of the Limping Child

• see Pediatrics, P91

Epiphyseal Injury

Table 23. Salter-Harris Classification of Epiphyseal Injury

<table>
<thead>
<tr>
<th>SALT(E)R–Harris Type</th>
<th>Description</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>I (Straight through; Stable)</td>
<td>Transverse through growth plate</td>
<td>Closed reduction and cast immobilization (except SCFE – ORIF); heals well, 95% do not affect growth</td>
</tr>
<tr>
<td>II (Above)</td>
<td>Through metaphysis and along growth plate</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>III (Low)*</td>
<td>Through epiphysis to plate and along growth plate</td>
<td>Anatomic reduction by ORIF to prevent growth arrest, avoid fixation across growth plate</td>
</tr>
<tr>
<td>IV (Through and through)*</td>
<td>Through epiphysis and metaphysis</td>
<td>Closed reduction and cast if anatomic; otherwise ORIF</td>
</tr>
<tr>
<td>V (Ram)*</td>
<td>Crush injury of growth plate</td>
<td>High incidence of growth arrest; no specific treatment</td>
</tr>
</tbody>
</table>

* Types III – IV are more likely to cause growth arrest and progressive deformity

Slipped Capital Femoral Epiphysis

• type I Salter-Harris epiphyseal injury at proximal hip
• most common adolescent hip disorder, peak incidence at pubertal growth spurt
• risk factors: male, obese (#1 factor), hypothyroid (risk of bilateral involvement)

Etiology

• multifactorial
  ▪ genetic: autosomal dominant, blacks > caucasians
  ▪ cartilaginous physis hypertrophies too rapidly under growth hormone effects
  ▪ sex hormone secretion, which stabilizes physis, has not yet begun
  ▪ overweight: mechanical stress
  ▪ trauma: causes acute slip

Clinical Features

• acute: sudden, severe pain with limp
• chronic (typically): groin and anterior thigh pain, may present with knee pain
  ▪ positive Trendelenburg sign on affected side, due to weakened gluteal muscles
• tender over joint capsule
• restricted internal rotation, abduction, flexion
  ▪ Whitman’s sign: obligatory external rotation during passive flexion of hip
• Loder classification: stable vs. unstable (provides prognostic information)
  ▪ unstable means patient cannot ambulate even with crutches

Investigations

• x-ray: AP, frog-leg, lateral radiographs both hips
  ▪ posterior and medial slip of epiphysis
  ▪ disruption of Klein’s line
  ▪ AP view may be normal or show widened/lucent growth plate compared with opposite side

Treatment

• operative
  ▪ mild/moderate slip: stabilize physis with pins in current position
  ▪ severe slip: ORIF or pin physis without reduction and osteotomy after epiphyseal fusion

Complications

• AVN (roughly half of unstable hips), chondrolysis (loss of articular cartilage, resulting in narrowing of joint space), pin penetration, premature OA, loss of ROM
Developmental Dysplasia of the Hip

- abnormal development of hip resulting in dysplasia and subluxation/dislocation of hip
- most common orthopedic disorder in newborns

Etiology
- due to ligamentous laxity, muscular underdevelopment, and abnormal shallow slope of acetabular roof
- spectrum of conditions that lead to hip subluxation and dislocation
  - dislocated femoral head completely out of acetabulum
  - dislocatable head in socket
  - head subluxates out of joint when provoked
  - dysplastic acetabulum, more shallow and more vertical than normal
- painless (if painful suspect septic dislocation)

Physical Exam
- diagnosis is clinical
  - limited abduction of the flexed hip (<50-60°)
  - affected leg shortening results in asymmetry in skin folds and gluteal muscles, wide perineum
  - Barlow’s test (for dislocatable hip)
    - flex hips and knees to 90° and grasp thigh
    - fully adduct hips, push posteriorly to try to dislocate hips
  - Ortolani’s test (for dislocated hip)
    - initial position as above but try to reduce hip with fingertips during abduction
    - positive test: palpable clunk is felt (not heard) if hip is reduced
  - Galeazzi’s sign
    - knees at unequal heights when hips and knees flexed
    - dislocated hip on side of lower knee
  - difficult test if child <1 yr
  - Trendelenburg test and gait useful if older (>2 yr)

Investigations
- U/S in first few months to view cartilage (bone is not calcified in newborns until 4-6 mo)
- follow up radiograph after 3 mo
- x-ray signs (at 4-6 mo): false acetabulum, acetabular index >25°, broken Shenton’s line, femoral neck above Hilgenreiner’s line, ossification centre outside of inner lower quadrant (quadrants formed by intersection of Hilgenreiner’s and Perkin’s line)

Treatment
- 0-6 mo: reduce hip using Pavlik harness to maintain abduction and flexion
- 6-18 mo: reduction under GA, hip spica cast x 2-3 mo (if Pavlik harness fails)
- >18 mo: open reduction; pelvic and/or femoral osteotomy

Complications
- redislocation, inadequate reduction, stiffness
- AVN of femoral head

Legg-Calvé-Perthes Disease (Coxa Plana)

- idiopathic AVN of femoral head, presents at 4-8 yr of age
- 12% bilateral, M>F = 5:1, 1/1,200
- associations
  - family history
  - low birth weight
  - abnormal pregnancy/delivery
  - ADHD in 33% of cases, delayed bone age in 89%
  - second-hand smoke exposure
  - Asian, Inuit, Central European
- key features
  - AVN of proximal femoral epiphysis, abnormal growth of the physis, and eventual remodelling of regenerated bone

Clinical Features
- child with antalgic or Trendelenburg gait ± pain
- intermittent knee, hip, groin, or thigh pain
- flexion contracture (stiff hip): decreased internal rotation and abduction of hip
- limb length discrepancy (late)
Investigations
• x-ray: AP pelvis, frog leg laterals
  ▪ may be negative early (if high index of suspicion, move to bone scan or MRI)
  ▪ eventually, characteristic collapse of femoral head (diagnostic)

Treatment
• goal is to preserve ROM and keep femoral head contained in acetabulum
• non-operative
  ▪ physiotherapy: ROM exercises
  ▪ brace in flexion and abduction x 2-3 yr (controversial)
• non-operative
  ▪ femoral or pelvic osteotomy (>8 yr of age or severe)
    ▪ prognosis better in males, <5 yr, <50% of femoral head involved, abduction >30°
  ▪ 60% of involved hips do not require operative intervention
  ▪ natural history is early onset OA and decreased ROM

Osgood-Schlatter Disease
• inflammation of patellar ligament at insertion point on tibial tuberosity
• M>F
• age of onset: boys 12-15 yr; girls 8-12 yr

Mechanism
• repetitive tensile stress on insertion of patellar tendon over the tibial tuberosity causes minor
  avulsion at the site and subsequent inflammatory reaction (tibial tubercle apophysitis)

Clinical Features
• tender lump over tibial tuberosity
• pain on resisted leg extension
• anterior knee pain exacerbated by jumping or kneeling, relieved by rest

Investigations
• x-ray: lateral knee: fragmentation of the tibial tubercle, ± ossicles in patellar tendon

Treatment
• benign, self-limited condition, does not resolve until growth halts
• majority non-operative
  ▪ may restrict activities such as basketball or cycling
  ▪ NSAIDs, rest, flexibility, isometric strengthening exercises
  ▪ casting if symptoms do not resolve with conservative management
• operative: ossicle excision in refractory cases (patient is skeletally mature with persistent
  symptoms)

Congenital Talipes Equinovarus (Club Foot)
• congenital foot deformity
• muscle contractures resulting in CAVE deformity
• bony deformity: talar neck medial and plantar deviated; varus calcaneus and rotated medially
  around talus; navicular and cuboid medially displaced
• 1-2/1,000 newborns, 50% bilateral, occurrence M>F, severity F>M

Etiology
• intrinsic causes (neurologic, muscular, or connective tissue diseases) vs. extrinsic (intrauterine
  growth restriction), may be idiopathic, neurogenic, or syndrome-associated
• fixed deformity

Physical Exam
• examine hips for associated DDH
• examine knees for deformity
• examine back for dysraphism (unfused vertebral bodies)

Treatment
• largely non-operative via Ponseti Technique (serial manipulation and casting)
  ▪ correct deformities in CAVE order
    ▪ change strapping/cast q1-2wk
    ▪ surgical release in refractory case (rare)
      ▪ delayed until 3-4 mo of age
• 3 yr recurrence rate = 5-10%
• mild recurrence common; affected foot is permanently smaller/stiffer than normal foot with calf
  muscle atrophy
**Scoliosis**

- lateral curvature of spine with vertebral rotation
- age: 10-14 yr
- more frequent and more severe in females

**Etiology**
- idiopathic: most common (90%)
- congenital: vertebrae fail to form or segment
- neuromuscular: UMN or LMN lesion, myopathy
- postural: leg length discrepancy, muscle spasm
- other: osteochondrodystrophies, neoplastic, traumatic

**Clinical Features**
- ± back pain
- primary curve where several vertebrae affected
- secondary curves above and below fixed 1st curve to try and maintain normal position of head and pelvis
- asymmetric shoulder height when bent forward
- Adam's test: rib hump when bent forward
- prominent scapulae, creased flank, asymmetric pelvis
- associated posterior midline skin lesions in neuromuscular scolioses
  - café-au-lait spots, dimples, neurofibromas
  - axillary freckling, hemangiomas, hair patches
- associated pes cavus or leg atrophy
- apparent leg length discrepancy

**Investigations**
- x-ray: 3-foot standing, AP, lateral
  - measure curvature: Cobb angle
  - may have associated kyphosis

**Treatment**
- based on Cobb angle
  - <25°: observe for changes with serial radiographs
  - >25° or progressive: bracing (many types) that halt/slow curve progression but do NOT reverse deformity
  - >45°, cosmetically unacceptable or respiratory problems: surgical correction (spinal fusion)

**Bone Tumours**

- primary bone tumours are rare after 3rd decade
- metastases to bone are relatively common after 3rd decade

**Clinical Features**
- malignant (primary or metastasis): local pain and swelling (wk – mo), worse on exertion and at night, ± soft tissue mass
- benign: usually asymptomatic
- minor trauma often initiating event that calls attention to lesion

**Table 24. Distinguishing Benign from Malignant Bone Lesions on X-Ray**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>No periosteal reaction</td>
<td>Acute periosteal reaction</td>
</tr>
<tr>
<td></td>
<td>• Codman’s triangle</td>
</tr>
<tr>
<td></td>
<td>• “Onion skin”</td>
</tr>
<tr>
<td></td>
<td>• “Sunburst”</td>
</tr>
<tr>
<td>Thick endosteal reaction</td>
<td>Broad border between lesion and normal bone</td>
</tr>
<tr>
<td>Well developed bone formation</td>
<td>Varied bone formation</td>
</tr>
<tr>
<td>Intraosseous and even calcification</td>
<td>Extraosseous and irregular calcification</td>
</tr>
</tbody>
</table>


**Diagnosis**
- routine x-ray findings
  - location (which bone, diaphysis, metaphysis, epiphysis)
  - size
  - lytic/lucent vs. sclerotic
  - involvement (cortex, medulla, soft tissue)
• matrix (radiolucent, radiodense or calcified)
• periosteal reaction
• margin (geographic vs. permeative)
• any pathological fracture
• soft tissue swelling
• malignancy is suggested by rapid growth, warmth, tenderness, lack of sharp definition
• staging should include
  • blood work including liver enzymes
  • CT chest
  • bone scan
  • bone biopsy
    • should be referred to specialized centre prior to biopsy
    • classified into benign, benign aggressive, and malignant
  • MRI of affected bone

Benign Active Bone Tumours

BONE-FORMING TUMOURS

Osteoid Osteoma
• bone tumour arising from osteoblasts
• peak incidence in 2nd and 3rd decades, M:F = 2:1 (young males)
• proximal femur and tibia diaphysis most common locations
• not known to metastasize
• radiographic findings: small, round radiolucent nidus (<1.5 cm) surrounded by dense sclerotic bone (“bull’s-eye”)
• symptoms: produces severe intermittent pain from prostaglandin secretion and COX1/2 expression, mostly at night (diurnal prostaglandin production), thus is characteristically relieved by NSAIDs
• treatment: NSAIDs for night pain; surgical resection of nidus

FIBROUS LESIONS

Fibrous Cortical Defect
• or non-ossifying fibroma; fibrous bone lesion
• most common benign bone tumour in children, typically asymptomatic and an incidental finding
• occur in as many as 35% of children, peak incidence between 2-25 yr old, higher prevalence in males
• femur and proximal tibia most common locations, 50% of patients have multiple defects usually bilateral, symmetrical
• radiographic findings: diagnostic, metaphyseal eccentric ‘bubbly’ lytic lesion near physis; thin smooth/lobulated well-defined sclerotic margin
• treatment: most lesions resolve spontaneously

Osteochondroma
• cartilage capped bony tumour
• 2nd and 3rd decades, M:F = 1.8:1
• most common of all benign bone tumours – 45%
• 2 types: sessile (broad based and increased risk of malignant degeneration) vs. pedunculated (narrow stalk)
• metaphysis of long bone near tendon attachment sites (usually distal femur, proximal tibia, or proximal humerus)
  • radiographic findings: cartilage-capped bony spur on surface of bone (“mushroom” on x-ray)
  • may be multiple (hereditary, autosomal dominant form) – higher risk of malignant change
• generally very slow growing and asymptomatic unless impinging on neurovascular structure (‘painless mass’)
• growth usually ceases when skeletal maturity is reached
• malignant degeneration occurs in 1-2% (becomes painful or rapidly grows)
• treatment: typically observation; surgical excision if symptomatic

Enchondroma
• hyaline cartilage tumour; majority asymptomatic, presenting as incidental finding or pathological fracture
• 2nd and 3rd decades
• 60% occur in the small tubular bones of the hand and foot; others in femur (20%), humerus, ribs

Figure 57. T1 MRI of femoral enchondroma
• benign cartilagenous growth, an abnormality of chondroblasts, develops in medullary cavity
  ▪ single/multiple enlarged rarefied areas in tubular bones
  ▪ lytic lesion with sharp margination and irregular central calcification (stippled/punctate/popcorn appearance)
• malignant degeneration to chondrosarcoma occurs in 1-2% (pain in absence of pathologic fracture is an important clue)
• not known to metastasize
• treatment: observation with serial x-rays; surgical curettage if symptomatic or lesion grows

CYSTIC LESIONS

Unicameral/Solitary Bone Cyst
• most common cystic lesion; serous fluid filled lesion
• children and young adults, peak incidence during first 2 decades, M:F = 2:1
• proximal humerus and femur most common
• symptoms: asymptomatic, or local pain; complete pathological fracture (50% presentations) or incidental detection
• radiographic findings: lytic translucent area on metaphyseal side of growth plate, cortex thinned/expanded; well defined lesion
• treatment: aspiration followed by steroid injection; curettage ± bone graft indicated if re-fracture likely

Benign Aggressive Bone Tumours

Giant Cell Tumours/Aneurysmal Bone Cyst/Osteoblastoma
• affects patients of skeletal maturity, peak 3rd decade
• osteoblastoma: found in the distal femur, proximal tibia, distal radius, sacrum, tarsal bones, spine
• giant cell tumour: pulmonary metastases in 3%
• aneurysmal bone cysts: either solid with fibrous/granular tissue, or blood-filled
• radiographic findings
  ▪ giant cell tumour: eccentric lytic lesions, in epiphyses adjacent to subchondral bone; may break through cortex; T2 MRI enhances fluid within lesion (hyper-intense signal)
  ▪ aneurysmal bone cyst: expanded with honeycomb shape
  ▪ osteoblastoma: often nonspecific; calcified central nidus (>2 cm) with radiolucent halo and sclerosis
• symptoms: local tenderness and swelling, pain may be progressive (giant cell tumours), ± symptoms of nerve root compression (osteoblastoma)
• 15% recur within 2 yr of surgery

Treatment
• intralesional curettage + bone graft or cement
• wide local excision of expendable bones

Malignant Bone Tumours

<table>
<thead>
<tr>
<th>Age</th>
<th>Tumour</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>Neuroblastoma</td>
</tr>
<tr>
<td>1-10</td>
<td>Ewing’s of tubular bones</td>
</tr>
<tr>
<td>10-30</td>
<td>Osteosarcoma, Ewing’s of flat bones</td>
</tr>
<tr>
<td>30-40</td>
<td>Reticulum cell sarcoma, fibrosarcoma, periosteal osteosarcoma, malignant giant cell tumour, lymphoma</td>
</tr>
<tr>
<td>&gt;40</td>
<td>Metastatic carcinoma, multiple myeloma, chondrosarcoma</td>
</tr>
</tbody>
</table>

Osteosarcoma
• malignant bone tumour
• most frequently diagnosed in 2nd decade of life (60%), 2nd most common primary malignancy in adults
• history of Paget’s disease (elderly patients), previous radiation treatment
• predilection for sites of rapid growth: distal femur (45%), proximal tibia (20%), and proximal humerus (15%)
  ▪ invasive, variable histology; frequent metastases without treatment (lung most common)
• painful symptoms: progressive pain, night pain, poorly defined swelling, decreased ROM
• radiographic findings
  ▪ characteristic periosteal reaction: Codman’s triangle (see Figure 56) or “sunburst” spicule formation (tumour extension into periosteum)
  ▪ destructive lesion in metaphysis may cross epiphyseal plate
• management: complete resection (limb salvage, rarely amputation), neo-adjuvant chemo; bone scan – rule out skeletal metastases, CT chest – rule out pulmonary metastases
• prognosis: 70% (high-grade); 90% (low-grade)

Chondrosarcoma
• malignant chondrogenic tumour
• primary (2/3 cases)
  • previous normal bone, patient >40 yr; expands into cortex to give pain, pathological fracture, flecks of calcification
• secondary (1/3 cases)
  • malignant degeneration of pre-existing cartilage tumour such as enchondroma or osteochondroma
  • age range 25-45 yr and better prognosis than primary chondrosarcoma
• symptoms: progressive pain, uncommonly palpable mass
• radiographic findings: in medullary cavity, irregular “popcorn” calcification
• treatment: unresponsive to chemotherapy, treat with aggressive surgical resection + reconstruction; regular follow-up x-rays of resection site and chest
• prognosis: 10-yr survival 90% low-grade, 20-40% high-grade

Ewing’s Sarcoma
• malignant small round cell sarcoma
• most occur between 5-25 yr old
• florid periosteal reaction in metaphyses of long bone with diaphysal extension
• metastases frequent without treatment
• signs/symptoms: presents with pain, mild fever, erythema and swelling, anemia, increased WBC, ESR, LDH (mimics an infection)
• radiographic findings: moth-eaten appearance with periosteal lamellated pattern (“onion-skinning”)
• treatment: resection, chemotherapy, radiation
• prognosis – 70%, worst prognostic factor is distant metastases

Multiple Myeloma
• proliferation of neoplastic plasma cells
• most common primary malignant tumour of bone in adults (~43%)
• 90% occur in people >40 yr old, M:F = 2:1, African-Americans (twice as common)
• signs/symptoms: localized bone pain (cardinal early symptom), compression/pathological fractures, renal failure, nephritis, high incidence of infections (e.g. pyelonephritis/pneumonia), systemic (weakness, weight loss, anorexia)
• labs: anemia, thrombocytopenia, increased ESR, hypercalcemia, increased Cr
• radiographic findings: multiple, “punched-out” well-demarcated lesions, no surrounding sclerosis, marked bone expansion
• diagnosis
  • serum/urine immunoelectrophoresis (monoclonal gammopathy)
  • CT-guided biopsy of lytic lesions at multiple bony sites
• treatment: chemotherapy, bisphosphonates, radiation, surgery for symptomatic lesions or impending fractures – debulking, internal fixation
• prognosis: 5 yr survival 30%; 10 yr survival 11%
• see Hematology, H49

Bone Metastases
• most common cause of bone lesions in adults; typically age >40
• 2/3 from breast or prostate; also consider thyroid, lung, kidney
• usually osteolytic; prostate occasionally osteoblastic
• may present with mechanical pain and/or night pain, pathological fracture, hypercalcemia
• bone scan for MSK involvement, MRI for spinal involvement may be helpful
• treatment: pain control, bisphosphonates, stabilization of impending fractures if Mirel’s Criteria >8 (ORIF, IM rod, bone cement)

Table 26. Mirel’s Criteria for Impending Fracture Risk and Prophylactic Internal Fixation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number Assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
</tr>
<tr>
<td>Pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mild</td>
</tr>
<tr>
<td></td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
</tr>
<tr>
<td>Lesion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blastic</td>
</tr>
<tr>
<td></td>
<td>Mixed</td>
</tr>
<tr>
<td></td>
<td>Lytic</td>
</tr>
<tr>
<td>Size</td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1/3 bone diameter</td>
</tr>
<tr>
<td></td>
<td>1/3-2/3 diameter</td>
</tr>
<tr>
<td></td>
<td>&gt;2/3 diameter</td>
</tr>
</tbody>
</table>
# Common Medications

Table 27. Common Medications

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Dosing Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefazolin (Ancef®)</td>
<td>1-2 g IV q8h</td>
<td>Prophylactically before orthopedic surgery</td>
<td>First generation cephalosporin; do not use with penicillin allergy</td>
</tr>
<tr>
<td>heparin</td>
<td>5000 IU SC q12h</td>
<td>To prevent venous thrombosis and pulmonary emboli</td>
<td>Monitor platelets, follow PTT which should rise 1.5-2x</td>
</tr>
</tbody>
</table>
| LMWH | dalteparin (Fragmin®)  
enoxaparin (Lovenox®)  
fondaparinux (Arixtra®) | 5000 IU SC OD  
30-40 mg SC bid  
2.5 mg SC OD | DVT prophylaxis especially in hip and knee surgery | Fixed dose, no monitoring, improved bioavailability, increased bleeding rates |
| oral anticoagulants | dabigatran (Pradaxa®)  
rivaroxaban (Xarelto®)  
apixaban | 110 mg PO x1 then 220 mg PO OD  
10 mg PO OD  
2.5 mg PO bid | DVT prophylaxis especially TKA and THA | Predictable, no monitoring, oral administration; no antidote |
| midazolam (Versed®) | 0.02-0.04 mg/kg IV | Conscious sedation for short procedures | Medication used during fracture reduction – monitor for respiratory depression |
| fentanyl (Sublimaze®) | 0.5-3 µg/kg IV | Conscious sedation for short procedures | Short acting anesthetic used in conjunction with midazolam (Versed®) |
| triamcinolone (Aristocort®) – an injectable steroid | 0.5-1 mL of 25 mg/mL suspension | Suspension (injected into inflamed joint or bursa); amount varies by joint size | Potent anti-inflammatory effect; increased pain for 24 h; rarely causes fat necrosis and skin depigmentation |
| naproxen (Aleve®, Naprosyn®) | 250-500 mg bid | Pain due to inflammation, arthritis, soft tissue injury | NSAID, may cause gastric erosion and bleeding |
| misoprostol (Cytotec®) | 200 µg qid | Prophylaxis of HO after THA | Use with indomethacin |
| indomethacin (Indocid®) | 25 mg PO tid | Prophylaxis of HO after THA | Use with misoprostol |
| ibuprofen (Advil®, Motrin®) | 200-400 mg tid | Pain (including post-operative), inflammation (including arthritis) | NSAID, may cause gastric erosion and bleeding |
| propofol (Diprivan®) | 1-2 mg/kg IV maintenance 0.5 mg/kg | Conscious sedation for short procedures | Short acting anesthetic often used in conjunction with fentanyl (Sublimaze®) |
# Otolaryngology – Head & Neck Surgery

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- Throat
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Figure 7. Extratemporal segment of facial nerve
Branches of facial nerve (in order from superior to inferior)
To Zanzibar By Motor Car

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Branches of the external carotid artery (in order from inferior to superior)
Some Angry Lady Figured Out PMS

Figure 9. Anatomy of the neck

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Anatomical Triangles of the Neck

Anterior triangle
- bounded by anterior border of SCM, midline of neck, and lower border of mandible
- divided into
  - submental triangle: bounded by both anterior bellies of digastric and hyoid bone
  - digastric triangle: bounded by anterior and posterior bellies of digastric and inferior border of mandible
  - carotid triangle: bounded by sternocleidomastoid, anterior belly of omohyoid, and posterior belly of digastric
    - contains: tail of parotid, submandibular gland, hypoglossal nerve, carotid bifurcation, and lymph nodes

Posterior triangle
- bounded by posterior border of sternocleidomastoid, anterior border of trapezius, and middle third of clavicle
- divided into
  - occipital triangle: superior to posterior belly of the omohyoid
  - subclavian triangle: inferior to posterior belly of omohyoid
- contains: spinal accessory nerve and lymph nodes

Table 1. Lymphatic Drainage of Nodal Groups and Anatomical Triangles of Neck

<table>
<thead>
<tr>
<th>Nodal Group/Level</th>
<th>Location</th>
<th>Drainage</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Suboccipital (S)</td>
<td>Base of skull, posterior</td>
<td>Posterior scalp</td>
</tr>
<tr>
<td>2. Retroauricular (R)</td>
<td>Superficial to mastoid process</td>
<td>Scalp, temporal region, external auditory meatus, posterior pinna</td>
</tr>
<tr>
<td>3. Parotid-preauricular (P)</td>
<td>Anterior to ear</td>
<td>External auditory meatus, anterior pinna, soft tissue of frontal and temporal regions, root of nose, eyelids, palpebral conjunctiva</td>
</tr>
<tr>
<td>4. Submental (Level Ia)</td>
<td>Anterior bellies (midline) of digastric muscles, tip of mandible, and hyoid bone</td>
<td>Floor of mouth, anterior tongue, anterior mandibular alveolar ridge, lower lip</td>
</tr>
<tr>
<td>5. Submandibular (Level Ib)</td>
<td>Anterior belly of digastric muscle, stylohyoid muscle, body of mandible</td>
<td>Oral cavity, anterior nasal cavity, soft tissues of the mid-face, submandibular gland</td>
</tr>
<tr>
<td>6. Upper jugular (Levels IIA and IIB)</td>
<td>Skull base to inferior border of hyoid bone along SCM muscle</td>
<td>Oral cavity, nasal cavity, naso/oro/hypopharynx, larynx, parotid glands</td>
</tr>
<tr>
<td>7. Middle jugular (Level III)</td>
<td>Inferior border of hyoid bone to inferior border of cricoid cartilage along SCM muscle</td>
<td>Oral cavity, naso/oro/hypopharynx, larynx</td>
</tr>
<tr>
<td>8. Lower jugular* (Level IV)</td>
<td>Inferior border of cricoid cartilage to clavicle along SCM muscle</td>
<td>Hypopharynx, thyroid, cervical esophagus, larynx</td>
</tr>
<tr>
<td>9. Posterior triangle** (Levels VA and VB)</td>
<td>Posterior border of SCM, anterior border of trapezius, from skull base to clavicle</td>
<td>Nasopharynx and oropharynx, cutaneous structures of the posterior scalp and neck</td>
</tr>
<tr>
<td>10. Anterior compartment*** (Level VI)</td>
<td>Hyoid bone (midline) to suprasternal notch between the common carotid arteries</td>
<td>Thyroid gland, glottic and subglottic larynx, apex of piriform sinus, cervical esophagus</td>
</tr>
</tbody>
</table>

*Virchow node: left lower jugular (level IV) supraclavicular node
**Includes some supraclavicular nodes
***Includes pretracheal, precricoid, paramediastinal, and perithyroidal nodes

Paired Parasympathetic Ganglia of the Head and Neck
- Ciliary: pupillary constriction
- Pterygopalatine: lacrimal gland, nasal mucosa
- Submandibular: submandibular, sublingual glands
- Otic: parotid gland

Function of Facial Nerve
"Ears, Tears, Face, Taste"
- Ears: stapedius muscle
- Tears: lacrimation (lacrimal gland) and salivation (parotid)
- Face: muscles of facial expression
- Taste: sensory anterior 2/3 of tongue (via chorda tympani)

4 Strap Muscles of the Neck
- Thyrohyoid
- Omohyoid
- Sternohyoid
- Sternothyroid

Figure 10. Anatomy of the thyroid gland

*Thyroidea ima artery: present in 3% of population, arises from aortic arch or innominate artery

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Differential Diagnoses of Common Presenting Problems

**Dizziness**

- **Peripheral (Vestibular)**
  - Benign paroxysmal positional vertigo (BPPV)
  - Labyrinthitis
  - Meniere's disease
  - Vestibular neuritis
  - Autoimmune inner ear disease
  - Cholesteatoma
  - Ototoxic drug exposure
  - Perilymph fistula
  - Recurrent vestibulopathy
  - Superior semicircular canal dehiscence
  - Temporal bone fracture

- **Central**
  - Cerebrovascular disorders
    - Vertebrobasilar insufficiency
    - Transient ischemic attacks
    - Wallenberg's syndrome
    - Cerebellar infarction
    - Migraine vertigo
    - Multiple sclerosis
    - Inflammation
    - Meningitis
    - Cerebellar abscess
    - Trauma: cerebellar contusion
    - Toxic: alcohol, hypnotics, drugs
    - Tumours
    - CPA tumours
    - Posterior fossa tumours
    - Glomus tumours

- **Organic Diseases**
  - Cardiac
    - Arrhythmias
    - Aortic stenosis
    - Vasovagal
    - Orthostatic hypotension
    - Anemia
    - Periperal neuropathy
    - Visual impairment

- **Non-Vertiginous**
  - Depression
  - Anxiety
  - Panic disorder
  - Hyperventilation
  - Personality disorder
  - Phobic dizziness

**Common causes in bold**

True nystagmus and vertigo caused by a peripheral lesion will never last longer than a couple of weeks because of compensation. Central lesions do not compensate, hence nystagmus and vertigo will persist.

5 “D”s of Vertebrobasilar Insufficiency
- Drop attacks
- Diplopia
- Dysarthria
- Dizziness
- Dysphagia

**Figure 11. Differential diagnosis of dizziness**

**Otalgia**

- **External Ear**
  - Infection
    - Auricular cellulitis
    - External canal abscess
    - Herpes simplex/zoster
    - Otitis externa
    - Trauma
    - Burns
    - Frostbite
    - Hematoma
    - Lacerations
    - Other
    - Cerumen impaction
    - Foreign body
    - Neoplasm of external canal

- **Middle/Inner Ear**
  - Infection
    - AOM
    - Mastoiditis
    - Myringitis
    - Otitis media with effusion
    - Skull base infections
    - Trauma
    - Barotrauma
    - Traumatic perforation
    - Other
    - Cholesteatoma
    - Neoplasm
    - Wegener's granulomatosis

- **Referred Pain**
  - Infection
    - Ramsay Hunt syndrome
    - Tonsilitis
    - Tracheitis
    - Trauma
    - Cervical arthritis
    - Thyroiditis
    - Other
    - Glossopharyngeal neuralgia
    - Neoplasm of oral cavity, larynx, pharynx
    - Teeth
    - TMJ syndrome
    - Trismus

**Figure 12. Differential diagnosis of otalgia**
Hearing Loss

Figure 13. Differential diagnosis of hearing loss

Tinnitus

Figure 14. Differential diagnosis of tinnitus
**Nasal Obstruction**

Table 2. Differential Diagnosis of Nasal Obstruction

<table>
<thead>
<tr>
<th>Acquired</th>
<th>Congenital</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nasal Cavity</td>
<td>Nasal Cavity</td>
</tr>
<tr>
<td>• Rhinitis</td>
<td>• Nasal dermoid cyst</td>
</tr>
<tr>
<td>• Acute/chronic</td>
<td>• Encephalocele</td>
</tr>
<tr>
<td>• Vasomotor</td>
<td>• Gioma</td>
</tr>
<tr>
<td>• Allergic</td>
<td>• Choanal atresia</td>
</tr>
<tr>
<td>Rhinosinusitis</td>
<td></td>
</tr>
<tr>
<td>• Foreign bodies</td>
<td></td>
</tr>
<tr>
<td>• Enlarged turbinates</td>
<td></td>
</tr>
<tr>
<td>• Tumour</td>
<td></td>
</tr>
<tr>
<td>• Benign: polyps, inverting papilloma</td>
<td></td>
</tr>
<tr>
<td>• Malignant</td>
<td></td>
</tr>
<tr>
<td>• SCC</td>
<td></td>
</tr>
<tr>
<td>• Esthesioneuroblastoma (olfactory neuroblastoma)</td>
<td></td>
</tr>
<tr>
<td>• Adenocarcinoma</td>
<td></td>
</tr>
<tr>
<td>Nasal Septum</td>
<td>Nasal Septum</td>
</tr>
<tr>
<td>• Septal deviation</td>
<td>• Septal deviation</td>
</tr>
<tr>
<td>• Septal hematoma/abscess</td>
<td>• Septal hematoma/abscess</td>
</tr>
<tr>
<td>• Dislocated septum</td>
<td>• Dislocated septum</td>
</tr>
<tr>
<td>Nasopharynx</td>
<td></td>
</tr>
<tr>
<td>• Adenoid hypertrophy</td>
<td></td>
</tr>
<tr>
<td>• Tumour</td>
<td>• Benign: juvenile nasopharyngeal angiofibroma (JNA), polyps</td>
</tr>
<tr>
<td>• Malignant</td>
<td>• Malignant: nasopharyngeal carcinoma</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
</tr>
<tr>
<td>• Granulomatous diseases, diabetes, vasculitis</td>
<td></td>
</tr>
</tbody>
</table>

**Hoarseness**

Table 3. Differential Diagnosis of Hoarseness

<table>
<thead>
<tr>
<th>Infectious</th>
<th>Neoplasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Acute/chronic laryngitis</td>
<td>• Benign tumour</td>
</tr>
<tr>
<td>• Laryngotracheobronchitis (croup)</td>
<td>• Papillomas (HPV infection)</td>
</tr>
<tr>
<td></td>
<td>• Minor salivary gland tumours</td>
</tr>
<tr>
<td></td>
<td>• Other</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Malignant tumours (e.g. thyroid)</td>
</tr>
<tr>
<td>• GERD</td>
<td>• SCC</td>
</tr>
<tr>
<td>• Vocal cord polyps/nodules</td>
<td>• Other</td>
</tr>
<tr>
<td>• Lifestyle: smoking, chronic EtOH use</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>• External laryngeal trauma</td>
<td></td>
</tr>
<tr>
<td>• Endoscopy and endotracheal tube (e.g. intubation granuloma)</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
<td></td>
</tr>
<tr>
<td>• Benign tumour</td>
<td>Malignant tumours (e.g. thyroid)</td>
</tr>
<tr>
<td>• Papillomas (HPV infection)</td>
<td>• SCC</td>
</tr>
<tr>
<td>• Minor salivary gland tumours</td>
<td>• Other</td>
</tr>
<tr>
<td>• Other</td>
<td></td>
</tr>
<tr>
<td>Cysts</td>
<td>Connective tissue disease</td>
</tr>
<tr>
<td>Systemic</td>
<td>RA</td>
</tr>
<tr>
<td>• Retention cysts</td>
<td>SLE</td>
</tr>
<tr>
<td>Neurologic (vocal cord paralysis due to superior ± recurrent laryngeal nerve injury)</td>
<td></td>
</tr>
<tr>
<td>• Central lesions</td>
<td>iatrogenic injury: thyroid, parathyroid surgery, carotid endarterectomy, patent ductus arteriosus (PDA) ligation</td>
</tr>
<tr>
<td>• Cerebrovascular accident (CVA)</td>
<td>Bilateral</td>
</tr>
<tr>
<td>• Head injury</td>
<td>iatrogenic injury: bilateral thyroid surgery, forceps delivery</td>
</tr>
<tr>
<td>• Multiple sclerosis (MS)</td>
<td>Neuromuscular</td>
</tr>
<tr>
<td>• Skull base tumours</td>
<td>• Myasthenia gravis</td>
</tr>
<tr>
<td>• Arnold-Chiari malformation</td>
<td></td>
</tr>
<tr>
<td>• Peripheral lesions</td>
<td></td>
</tr>
<tr>
<td>• Unilateral</td>
<td></td>
</tr>
<tr>
<td>• Lung malignancy</td>
<td></td>
</tr>
<tr>
<td>• Psychogenic aphonia (hysterical aphonia)</td>
<td></td>
</tr>
<tr>
<td>Functional</td>
<td></td>
</tr>
<tr>
<td>• Laryngomalacia</td>
<td></td>
</tr>
<tr>
<td>• Laryngeal web</td>
<td></td>
</tr>
<tr>
<td>• Laryngeal atresia</td>
<td></td>
</tr>
</tbody>
</table>

Lung malignancy is the most common cause of extralaryngeal vocal cord paralysis
Neck Mass

Inflammatory/Infections
- Reactive lymphadenopathy
- TB or atypical mycobacteria
- Infectious mononucleosis
- Abscesses
- Cat scratch fever
- Sarcoidosis
- Kawasaki disease
- HIV

Congenital
- Thyroglossal duct cyst
- Thyroid tumour/goitre
- Pyramidal lobe of thyroid gland
- Ranula

Neoplasic
- Branchial cleft cyst
- Cystic hygroma
- Lymphoma
- Thyroid
- Sarcoma
- Salivary gland neoplasm
- Rhabdomyosarcoma
- Neuroblastoma

Malignant
- Head and neck primary
- Infraclavicular primary
- Leukemia

Benign
- Salivary gland neoplasm
- Lipoma
- Fibroma
- Vascular

Hearing

Normal Hearing Physiology

- **Conductive pathway (external auditory canal to cochlea):** air conduction of sound energy down the EAC → vibration of the tympanic membrane (area effect) → sequential vibration of the middle ear ossicles: malleus, incus, stapes (lever effect) → transmission of amplified vibrations from the stapes footplate in the middle ear to the oval window of the cochlea in the inner ear → pressure differential on cochlear fluid creates movement along the basilar membrane within the cochlea from base to apex
- **Neural pathway (nerve to brain):** basilar membrane vibration stimulates overlying hair cells in the organ of Corti → stimulation of bipolar neurons in the spiral ganglion of the cochlear division of CN VIII → cochlear nucleus → superior olivary nucleus → lateral lemniscus → inferior colliculus → Sylvian fissure of temporal lobe

Types of Hearing Loss

1. **Conductive Hearing Loss**
   - conduction of sound to the cochlea is impaired
   - can be caused by external and middle ear disease

2. **Sensorineural Hearing Loss**
   - due to a defect in the conversion of sound into neural signals or in the transmission of those signals to the cortex
   - can be caused by disease of the inner ear (cochlea), acoustic nerve (CN VIII), brainstem, or cortex

3. **Mixed Hearing Loss**
   - combination of conductive and sensorineural hearing loss

**Auditory Acuity**
- whispered-voice test: mask one ear and whisper into the other
- tuning fork tests (see Table 4; audiogram is of greater utility)
- sensitivity depends on which tuning fork used (256 Hz, 512 Hz, 1024 Hz; 512 Hz has the greatest sensitivity)
  - **Rinne test**
    - 512 Hz tuning fork is struck and held firmly on mastoid process to test BC; the tuning fork is then placed beside the pinna to test AC
    - If AC > BC → positive Rinne (normal)
  - **Weber test**
    - 512 Hz tuning fork is held on vertex of head and patient states whether it is heard centrally (Weber negative) or is lateralized to one side (Weber right, Weber left)
    - can place vibrating fork on patient’s chin while they clench their teeth, or directly on teeth to elicit more reliable response
    - will only lateralize if difference in hearing loss between ears is >6 dB
### Pure Tone Audiometry

- A threshold is the lowest intensity level at which a patient can hear the tone 50% of the time.
- Thresholds are obtained for each ear at frequencies of 250, 500, 1000, 2000, 4000, and 8000 Hz.
- Air conduction thresholds are obtained with headphones and measure outer, middle, inner ear, and auditory nerve function.
- Bone conduction thresholds are obtained with bone conduction oscillators which bypass the outer and middle ear.

### Degree of Hearing Loss

- Determined on basis of the pure tone average (PTA) at 500, 1000, and 2000 Hz.

### Table 4. The Interpretation of Tuning Fork Tests

<table>
<thead>
<tr>
<th>Examples</th>
<th>Weber</th>
<th>Rinne</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal or bilateral sensorineural hearing loss</td>
<td>Central</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided conductive hearing loss, normal left ear</td>
<td>Lateralizes to right</td>
<td>BC &gt; AC (–) right</td>
</tr>
<tr>
<td>Right-sided sensorineural hearing loss, normal left ear</td>
<td>Lateralizes to left</td>
<td>AC &gt; BC (+) bilaterally</td>
</tr>
<tr>
<td>Right-sided severe sensorineural hearing loss or dead right ear, normal left ear</td>
<td>Lateralizes to left</td>
<td>BC &gt; AC (–) right*</td>
</tr>
</tbody>
</table>

*A vibrating tuning fork on the mastoid stimulates the cochlea bilaterally, therefore in this case the left cochlea is stimulated by the Rinne test on the right (e.g. a false negative test). These tests are not valid if the ear canals are obstructed with cerumen (e.g. will create conductive loss).

### Frequency of Tuning Fork

<table>
<thead>
<tr>
<th>Frequency (Hz)</th>
<th>Minimum Hearing Loss for Rinne to Reverse (BC &gt; AC, NEGATIVE Rinne) (dB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>256</td>
<td>15</td>
</tr>
<tr>
<td>512</td>
<td>30</td>
</tr>
<tr>
<td>1024</td>
<td>45</td>
</tr>
</tbody>
</table>

### Range of Frequencies Audible to Human Ear

- 20 to 20000 Hz
- Most sensitive frequencies: 1000 to 4000 Hz
- Range of human speech: 500 to 2000 Hz

### Hearing loss most often occurs at higher frequencies. Noise-induced (occupational) HL is classically seen at 4000 Hz. HL associated with otosclerosis is seen at 2000 Hz (Carhart’s notch).

### PURE TONE PATTERNS

1. **Conductive Hearing Loss** (Figure 16B and 16C)
   - BC in normal range
   - AC outside of normal range
   - Gap between AC and BC thresholds > 10 dB (an air-bone gap)

2. **Sensorineural Hearing Loss** (Figure 16D and 16E)
   - Both air and bone conduction thresholds below normal
   - Gap between AC and BC < 10 dB (no air-bone gap)

3. **Mixed Hearing Loss**
   - Both air and bone conduction thresholds below normal
   - Gap between AC and BC thresholds > 10 dB (an air-bone gap)
Speech Audiometry

Speech Reception Threshold
- lowest hearing level at which patient is able to repeat 50% of two syllable words which have equal emphasis on each syllable (spondee words)
- SRT and best pure tone threshold in the 500 to 2000 Hz range (frequency range of human speech) usually agree within 5 dB; if not, suspect a retrocochlear lesion or functional hearing loss
- used to assess the reliability of the pure tone audiometry

Speech Discrimination Test
- percentage of words the patient correctly repeats from a list of 50 monosyllabic words
- tested at 40 dB above the patient’s SRT, therefore degree of hearing loss is taken into account
- patients with normal hearing or conductive hearing loss score >90%
- score depends on extent of SNHL
- rollover effect: a decrease in discrimination as sound intensity increases; typical of a retrocochlear lesion (e.g. acoustic neuroma)
- investigate further if scores differ more than 20% between ears as asymmetry may indicate a retrocochlear lesion
- used as best predictor of hearing aid response: a poor discrimination score indicates significant neural degeneration and hearing aids may not be the best option for the patient

Impedance Audiometry

Tympnogram
- the Eustachian tube equalizes the pressure between the external and middle ear
- tympanograms graph the compliance of the middle ear system against a pressure gradient ranging from to –400 to +200 mmH₂O
- tympanogram peak occurs at the point of maximum compliance: where the pressure in the external canal is equivalent to the pressure in the middle ear
- normal range: –100 to +50 mmH₂O

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>High compliance</td>
</tr>
<tr>
<td></td>
<td>Normal pressure peak at 0</td>
</tr>
<tr>
<td></td>
<td>Note: with otosclerosis, peak is still at 0 mmH₂O but has a lower amplitude</td>
</tr>
<tr>
<td></td>
<td>Note: with ossicular chain discontinuity, peak is still at 0 mmH₂O but has a higher amplitude</td>
</tr>
<tr>
<td>B</td>
<td>No pressure peak</td>
</tr>
<tr>
<td></td>
<td>Poor TM mobility indicative of middle ear effusion (OME) or perforated TM</td>
</tr>
<tr>
<td>C</td>
<td>Negative pressure peak</td>
</tr>
<tr>
<td></td>
<td>Indicative of Eustachian tube dysfunction or early stage otitis media without effusion</td>
</tr>
</tbody>
</table>

Figure 17. Tympnograms

Static Compliance
- volume measurement reflecting overall stiffness of the middle ear system
- normal range: 0.3-1.6 cc
- negative middle ear pressure and abnormal compliance indicate middle ear pathology
- in a type B curve, ear canal volumes of >2 cc in children and 2.5 cc in adults indicate TM perforation or presence of a patent ventilation tube

Acoustic Stapedial Reflexes
- stapedius muscle contracts in response to loud sound
- **acoustic reflex threshold** = 70-100 dB greater than hearing threshold; if hearing threshold >85 dB, reflex likely absent
- stimulating either ear causes bilateral and symmetrical reflexes
- for reflex to be present, CN VII must be intact and no conductive hearing loss in monitored ear
- if reflex is absent without conductive or severe sensorineural loss, suspect CN VII lesion
- **acoustic reflex decay test** = ability of stapedius muscle to sustain contraction for 10 s at 10 dB
- normally, little reflex decay occurs at 500 and 1000 Hz
- with cochlear hearing loss, acoustic reflex thresholds are 25-60 dB
- with retrocochlear hearing loss (acoustic neuroma), absent acoustic reflexes or marked reflex decay (>50%) within 5 s
Auditory Brainstem Response

- measures neuroelectric potentials (waves) in response to a stimulus in five different anatomic sites (see Order of Neural Pathway sidebar on OT9); this test can be used to determine the site of lesion
- delay in brainstem response suggests cochlear or retrocochlear abnormalities
- does not require volition or co-operation of patient (therefore of value in children and in malingers)

Otoacoustic Emissions

- objective test of hearing where a series of clicks is presented to the ear and the cochlea generates an echo which can be measured
- often used in newborn screening
- can be used to uncover normal hearing in malingers
- absence of emissions can be due to hearing loss or fluid in the middle ear

Aural Rehabilitation

- dependent on degree of hearing loss, communicative requirements, motivation, expectations, and physical and mental abilities
- negative prognostic factors
  - poor speech discrimination
  - narrow dynamic range (recruitment)
  - unrealistic expectations
- types of hearing aids
  - BTE: behind-the-ear (with occlusive mould or open fit which allows natural sound to pass – for milder hearing losses)
  - ITE: in-the-ear, placed in concha
  - ITC: in-the-canal, placed entirely in ear canal
  - CIC: contained-in-canal, placed deeply in ear canal
  - bone conduction – bone-anchored hearing aid (BAHA): attached to the skull
  - contralateral routing of signals (CROS)
- assistive listening devices
  - direct/indirect audio output
  - infrared, FM radio, or induction loop systems
  - telephone, television, or alerting devices
- cochlear implants
  - electrode is inserted into the cochlea to allow direct stimulation of the auditory nerve
  - for profound bilateral sensorineural hearing loss not rehabilitated with conventional hearing aids
  - established indication: post-lingually deafened adults, pre- and post-lingually deaf children

Vertigo

Evaluation of the Dizzy Patient

- vertigo: illusion of rotational, linear, or tilting movement of self or environment
  - vertigo is produced by peripheral (inner ear) or central (brainstem-cerebellum) stimulation
  - it is important to distinguish vertigo from other disease entities that may present with similar complaints of “dizziness” (e.g. cardiovascular, psychiatric, neurological, aging)

<table>
<thead>
<tr>
<th></th>
<th>Peripheral</th>
<th>Central</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imbalance</td>
<td>Moderate-severe</td>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Nausea and Vomiting</td>
<td>Severe</td>
<td>Variable</td>
</tr>
<tr>
<td>Auditory Symptoms</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>Neurologic Symptoms</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Compensation</td>
<td>Rapid</td>
<td>Slow</td>
</tr>
<tr>
<td>Nystagmus</td>
<td>Unidirectional</td>
<td>Bidirectional</td>
</tr>
<tr>
<td></td>
<td>Horizontal or rotatory</td>
<td>Horizontal or vertical</td>
</tr>
</tbody>
</table>
Table 6. Differential Diagnosis of Vertigo Based on History

<table>
<thead>
<tr>
<th>Condition</th>
<th>Duration</th>
<th>Hearing Loss</th>
<th>Tinnitus</th>
<th>Aural Fullness</th>
<th>Other Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benign Paroxysmal Positional Vertigo (BPPV)</td>
<td>Seconds</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Menière’s Disease</td>
<td>Minutes to hours</td>
<td>Uni/bilateral, fluctuating</td>
<td>+</td>
<td>Pressure/warmth</td>
<td></td>
</tr>
<tr>
<td>Vestibular Neuronitis</td>
<td>Hours to days</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Labyrinthitis</td>
<td>Days</td>
<td>Unilateral</td>
<td>Whistling</td>
<td>–</td>
<td>Recent AOM</td>
</tr>
<tr>
<td>Acoustic Neuroma</td>
<td>Chronic</td>
<td>Progressive</td>
<td>+</td>
<td>–</td>
<td>Ataxia CN VII palsy</td>
</tr>
</tbody>
</table>

Table 7. Differential Diagnosis of Vertigo Based on Time Course

<table>
<thead>
<tr>
<th>Time Course</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent, lasting</td>
<td>BPPV</td>
</tr>
<tr>
<td>Single episode, lasting minutes to hours</td>
<td>Migraine, transient ischemia of the labyrinth or brainstem</td>
</tr>
<tr>
<td>Recurrent to hours</td>
<td>Menière’s</td>
</tr>
<tr>
<td>Prolonged</td>
<td>Vestibular neuritis, MS, brainstem/cerebellum infarct</td>
</tr>
<tr>
<td>Acoustic neuroma</td>
<td>Chronic</td>
</tr>
</tbody>
</table>

Benign Paroxysmal Positional Vertigo

Definition
- acute attacks of transient rotatory vertigo lasting seconds to minutes initiated by certain head positions, accompanied by torsional (i.e. rotatory) nystagmus (geotropic = fast phase towards the floor)
- most common form of positional vertigo (50% of patients with peripheral vestibular dysfunction)

Etiology
- due to canalithiasis (migration of free floating otoliths within the endolymph of the semicircular canal) or cupulolithiasis (otolith attached to the cupula of the semicircular canal)
  - can affect each of the 3 semicircular canals, although the posterior canal is affected in >90% of cases
  - causes: head injury, viral infection (URTI), degenerative disease, idiopathic
  - results in slightly different signals being received by the brain from the two balance organs resulting in sensation of movement

Diagnosis
- history (time course, provoking factors, associative symptoms)
- positive Dix-Hallpike maneuver (sensitivity 82%, specificity 71%)

Dix-Hallpike Positional Testing (see website for video and illustrations)
- the patient is rapidly moved from a sitting position to a supine position with the head hanging over the end of the table, turned to one side at 45° and neck extended 20° holding the position for 20 s
- onset of vertigo and rotary nystagmus indicate a positive test for the dependent side
- other diagnostic testing is not indicated in posterior canal BPPV

Treatment
- reassure patient that process resolves spontaneously
- particle repositioning maneuvers
  - Epley maneuver (performed by MD)
  - Brandt-Daroff exercises (performed by patient)
- surgery for refractory cases
- anti-emetics for N/V
- drugs to suppress the vestibular system delay eventual recovery and are therefore not used

Menière’s Disease (Endolymphatic Hydrops)

Definition
- episodic attacks of tinnitus, hearing loss, aural fullness, and vertigo lasting minutes to hours

Proposed Etiology
- inadequate absorption of endolymph leads to endolymphatic hydrops (over accumulation) that distorts the membranous labyrinth
Epidemiology
- peak incidence 40-60 yr
- bilateral in 35% of cases

Clinical Features
- episodic vertigo, fluctuating low frequency SNHL, tinnitus, and aural fullness
- ± drop attacks (Tumarkin crisis), ± N/V
- vertigo disappears with time (min to h), but hearing loss remains
- early in the disease: fluctuating SNHL
- later stages: persistent tinnitus and progressive hearing loss
- attacks come in clusters and can be debilitating to the patient
- triggers: high salt intake, caffeine, stress, nicotine, and alcohol

Treatment
- acute management may consist of bed rest, antiemetics, antivertiginous drugs (e.g. betahistine [Serc®]), and low molecular weight dextrans (not commonly used)
- long-term management may include
  - medical
    - low salt diet, diuretics (e.g. hydrochlorothiazide, triamterene, amiloride)
    - Serc® prophylactically to decrease intensity of attacks
    - local application of gentamicin to destroy vestibular end-organ, results in complete SNHL
  - surgical
    - selective vestibular neurectomy or transtympanic labyrinthectomy
    - vestibular implants have recently been introduced experimentally
- must monitor opposite ear as bilaterality occurs in 35% of cases

Vestibular Neuronitis

Definition
- acute onset of disabling vertigo often accompanied by N/V and imbalance without hearing loss that resolves over days leaving a residual imbalance that lasts days to weeks

Etiology
- thought to be due to a viral infection (e.g. measles, mumps, herpes zoster)
- ~30% of cases have associated URTI symptoms
- other: microvascular events, diabetes, autoimmune process
- considered to be the vestibular equivalent of Bell's palsy, sudden hearing loss, and acute vocal cord palsy

Clinical Features
- acute phase
  - severe vertigo with N/V and imbalance lasting 1-5 d
  - irritative nystagmus (fast phase towards the offending ear)
  - patient tends to veer towards affected side
- convalescent phase
  - imbalance and motion sickness lasting days to weeks
  - spontaneous nystagmus away from affected side
  - gradual vestibular adaptation requires weeks to months
- incomplete recovery likely with the following risk factors: elderly, visual impairment, poor ambulation
- repeated attacks can occur

Treatment
- acute phase
  - bed rest, vestibular sedatives (Gravol®), diazepam
- convalescent phase
  - progressive ambulation especially in the elderly
  - vestibular exercises: involve eye and head movements, sitting, standing, and walking

Labyrinthitis

Definition
- acute infection of the inner ear resulting in vertigo and hearing loss

Etiology
- may be serous (viral) or purulent (bacterial)
- occurs as a complication of acute and chronic otitis media, bacterial meningitis, cholesteatoma, and temporal bone fractures
- bacterial: S. pneumoniae, H. influenzae, M. catarrhalis, P. aeruginosa, P. mirabilis
- viral: rubella, CMV, measles, mumps, varicella zoster
Clinical Features
• sudden onset of vertigo, N/V, tinnitus, and unilateral hearing loss with no associated fever or pain
• meningitis is a serious complication

Investigations
• CT head
• if meningitis is suspected: lumbar puncture, blood cultures

Treatment
• treat with IV antibiotics, drainage of middle ear ± mastoidectomy

Acoustic Neuroma (Vestibular Schwannoma)

Definition
• schwannoma of the vestibular portion of CN VIII

Pathogenesis
• starts in the internal auditory canal and expands into cerebellopontine angle (CPA), compressing cerebellum and brainstem
• when associated with type 2 neurofibromatosis (NF2): bilateral acoustic neuromas, café-au-lait skin lesions, and multiple intracranial lesions

Clinical Features
• usually presents with unilateral SNHL (chronic) or tinnitus
• dizziness and unsteadiness may be present, but true vertigo is rare as tumour growth occurs slowly and thus compensation occurs
• facial nerve palsy and trigeminal (V1) sensory deficit (corneal reflex) are late complications
• risk factors: exposure to loud noise, childhood exposure to low-dose radiation, history of parathyroid adenoma

Diagnosis
• MRI with gadolinium contrast (gold standard)
• audiogram (to assess SNHL)
• poor speech discrimination relative to the hearing loss
• stapedial reflex absent or significant reflex decay
• ABR: increase in latency of the 5th wave
• vestibular tests: normal or asymmetric caloric weakness (an early sign)

Treatment
• expectant management if tumour is very small, or in elderly
• definitive management is surgical excision
• other options: gamma knife, radiation

Tinnitus

Definition
• an auditory perception in the absence of an acoustic stimuli, likely related to loss of input to neurons in central auditory pathways and resulting in abnormal firing

History
• subjective vs. objective (see Figure 14, OT7)
• continuous vs. pulsatile (vascular in origin)
• unilateral vs. bilateral
• associated symptoms: hearing loss, vertigo, aural fullness, otalgia, otorrhea

Investigations
• audiology
• if unilateral
  ▪ ABR, gadolinium enhanced MRI to exclude a retrocochlear lesion
  ▪ CT to diagnose glomus tympanicum (rare)
  ▪ MRI or angiogram to diagnose AVM
• if suspect metabolic abnormality: lipid profile, TSH

Treatment
• if a cause is found, treat the cause (e.g. drainage of middle ear effusion, embolization or excision of AVM)
• with no treatable cause: 50% will improve, 25% worsen, 25% remain the same
• avoid loud noise, ototoxic meds, caffeine, smoking
• tinnitus clinics
• identify situations where tinnitus is most bothersome (e.g. quiet times), mask tinnitus with soft music or “white noise”
• hearing aid if coexistent hearing loss
• tinnitus instrument: combines hearing aid with white noise masker
• trial of tocainamide

### Diseases of the External Ear

#### Cerumen Impaction

**Etiology**
- ear wax: a mixture of secretions from ceruminous and pilosebaceous glands, squames of epithelium, dust, and debris

**Risk Factors**
- hairy or narrow ear canals, in-the-ear hearing aids, cotton swab usage, osteomata

**Clinical Features**
- hearing loss (conductive)
- ± tinnitus, vertigo, otalgia, aural fullness

**Treatment**
- ceruminolytic drops (bicarbonate solution, olive oil, glycerine, Cerumenol®, Cerumenex®)
- syringing
- manual debridement (by MD)

#### Exostoses

**Definition**
- bony protuberances in the external auditory canal composed of lamellar bone

**Etiology**
- possible association with swimming in cold water

**Clinical Features**
- usually an incidental finding
- if large, they can cause cerumen impaction or otitis externa

**Treatment**
- no treatment required unless symptomatic

#### Otitis Externa

**Etiology**
- bacteria (~90% of OE): *Pseudomonas aeruginosa, Pseudomonas vulgaris, E. coli, S. aureus*
- fungus: *Candida albicans, Aspergillus niger*

**Risk Factors**
- associated with swimming (“swimmer’s ear”)
- mechanical cleaning (Q-tips®), skin dermatitis, aggressive scratching
- devices that occlude the ear canal: hearing aids, headphones, etc.
- allergic contact dermatitis, dermatologic conditions (psoriasis, atopic dermatitis)

**Clinical Features**
- acute
  - pain aggravated by movement of auricle (traction of pinna or pressure over tragus)
  - otorrhea (sticky yellow purulent discharge)
  - conductive hearing loss ± aural fullness 2° to obstruction of external canal by swelling and purulent debris
  - posterior auricular lymphadenopathy
  - complicated OE exists if the pinna and/or the periauricular soft tissues are erythematos and swollen
- chronic
  - pruritus of external ear ± excoriation of ear canal
  - atrophic and scaly epidermal lining, ± otorrhea, ± hearing loss
  - wide meatus but no pain with movement of auricle
  - tympanic membrane appears normal

---

Cerumen impaction is the most common cause of conductive hearing loss for those aged 15-50 yr

Syringing

**Indications**
- Totally occlusive cerumen with pain, decreased hearing, or tinnitus

**Contraindications**
- Active infection
- Previous ear surgery
- Only hearing ear
- TM perforation

**Complications**
- Otitis externa
- TM perforation
- Trauma
- Pain
- Vertigo
- Tinnitus
- Otitis media

**Method**
- Establish that TM is intact
- Gently pull the pinna superiorly and posteriorly
- Using warm water, aim the syringe nozzle upwards and posteriorly to irrigate the ear canal

Pulling on the pinna is extremely painful in otitis externa, but is usually well tolerated in otitis media
Treatment
- clean ear under magnification with irrigation, suction, dry swabbing, and C&S
- bacterial etiology
  - antipseudomonal otic drops (e.g. ciprofloxacin) or a combination of antibiotic and steroid (e.g. Cipro HC®)
  - do not use aminoglycoside if the tympanic membrane (TM) is perforated because of the risk of ototoxicity
  - introduction of fine gauze wick (pope wick) if external canal edematous
  - ± 3% acetic acid solution to acidify ear canal (low pH is bacteriostatic)
  - systemic antibiotics if either cervical lymphadenopathy or cellulitis is present
- fungal etiology
  - repeated debridement and topical antifungals (gentian violet, Mycostatin® powder, boric acid, Locacorten®, Vioform® drops)
- ± analgesics
- chronic otitis externa (pruritus without obvious infection) → corticosteroid alone (e.g. diprosalic acid)

Malignant (Necrotizing) Otitis Externa (Skull Base Osteomyelitis)

Definition
- osteomyelitis of the temporal bone

Epidemiology
- occurs in elderly diabetics and immunocompromised patients

Etiology
- rare complication of otitis externa
- *Pseudomonas* infection in 99% of cases

Clinical Features
- otalgia and purulent otorrhea that is refractory to medical therapy
- granulation tissue on the floor of the auditory canal

Complications
- cranial nerve palsy (most commonly CN VII>CN X>CN XI)
- systemic infection, death

Management
- imaging: high resolution temporal bone CT scan, gadolinium enhanced MRI, technetium scan
- requires hospital admission, debridement, IV antibiotics, hyperbaric O₂
- may require OR for debridement of necrotic tissue/bone

Diseases of the Middle Ear

Acute Otitis Media and Otitis Media with Effusion
- see Pediatric Otolaryngology, OT39

Chronic Otitis Media

Definition
- an ear with TM perforation in the setting of recurrent or chronic ear infections

Benign
- dry TM perforation without active infection

Chronic Serous Otitis Media
- continuous serous drainage (straw-coloured)

Chronic Suppurative Otitis Media
- persistent purulent drainage through a perforated TM
Cholesteatoma

Definition
- a cyst composed of keratinized desquamated epithelial cells occurring in the middle ear, mastoid, and temporal bone
- two types: congenital and acquired

Congenital
- presents as a “small white pearl” behind an intact tympanic membrane (anterior and medial to the malleus) or as a conductive hearing loss
- believed to be due to aberrant migration of external canal ectoderm during development
- not associated with otitis media/Eustachian tube dysfunction

Acquired (more common)
- primary cholesteatoma
  - frequently associated with retraction pockets in the pars flaccida (may lead to attic cholesteatomas which are difficult to visualize)
  - often has crusting or desquamated debris on lateral surface
- secondary cholesteatoma
  - pearly mass evident behind TM, frequently associated with marginal perforation
  - may appear as skin that have replaced the mucosa of the middle ear
- the associated chronic inflammatory process causes progressive destruction of surrounding bony structures

Clinical Features
- history of otitis media (especially if unilateral), ventilation tubes, ear surgery
- symptoms
  - progressive hearing loss (predominantly conductive although may get sensorineural hearing loss in late stage)
  - otalgia, aural fullness, fever
- signs
  - retraction pocket in TM, may contain keratin debris
  - TM perforation
  - granulation tissue, polyp visible on otoscopy
  - malodorous, unilateral otorrhea

Complications

| Table 8. Complications of Cholesteatoma |
|--------------------------------------|------------------|
| Local                                | Intracranial     |
| Ossicular erosion: conductive hearing loss | Meningitis       |
| Inner ear erosion: SNHL, dizziness, and/or labyrinthitis | Sigmoid sinus thrombosis |
| Temporal bone infection: mastoiditis, petrositis | Intracranial abscess (subdural, epidural, cerebellar) |
| Facial paralysis                      |                  |

Investigations
- audiogram and CT scan

Treatment
- there is no conservative therapy for cholesteatoma
- surgical: mastoidectomy ± tympanoplasty ± ossicular reconstruction

Mastoiditis

Definition
- infection (usually subperiosteal) of mastoid air cells, most commonly seen approximately two weeks after onset of untreated or inadequately treated acute suppurative otitis media
- more common in children than adults

Etiology
- acute mastoiditis caused by the same organisms as AOM: *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, *S. pyogenes*, *S. aureus*, *P. aeruginosa*

Clinical Features
- otorrhea
- tenderness to pressure over the mastoid
- retroauricular swelling with protruding ear
- fever, hearing loss, ± TM perforation (late)
- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)

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- CT radiologic findings: opacification of mastoid air cells by fluid and interruption of normal trabeculations of cells (coalescence)
Treatment
• IV antibiotics with myringotomy and ventilation tubes – usually all that is required acutely
• cortical mastoidectomy
  ▪ debridement of infected tissue allowing aeration and drainage
• indications for surgery
  ▪ failure of medical treatment after 48 h
  ▪ symptoms of intracranial complications
  ▪ aural discharge persisting for 4 wk and resistant to antibiotics

Otosclerosis
Definition
• fusion of stapes footplate to oval window so that it cannot vibrate

Etiology
• autosomal dominant, variable penetrance approximately 40%
• F>M, progresses during pregnancy (hormone responsive)

Clinical Features
• progressive conductive hearing loss first noticed in teens and 20s (may progress to sensorineural hearing loss if cochlea involved)
• ± pulsatile tinnitus
• tympanic membrane normal ± pink blush (Schwartz’s sign) associated with the neovascularization of otosclerotic bone
• characteristic dip at 2000 Hz (Carhart’s notch) on audiogram (see Figure 16C, OT10)

Treatment
• monitor with serial audiograms if coping with loss
• hearing aid (air conduction, bone conduction, BAHA)
• stapedectomy or stapedotomy (with laser or drill) with prosthesis is definitive treatment

Diseases of the Inner Ear

Congenital Sensorineural Hearing Loss

Hereditary Defects
• non-syndrome associated (70%)
  ▪ often idiopathic, autosomal recessive
  ▪ connexin 26 (GJB2) most common
• syndrome associated (30%)
  ▪ Waardenburg: white forelock, heterochromia iridis (each eye different colour), wide nasal bridge and increased distance between medial canthi
  ▪ Pendred: deafness associated with thyroid gland disorders, SLC26A4 gene, enlarged vestibular aqueducts
  ▪ Treacher-Collins: first and second branchial cleft anomalies
  ▪ Alport: hereditary nephritis

Prenatal TORCH Infections
• toxoplasmosis, others (e.g. HIV, syphilis), rubella, CMV, HSV

Perinatal
• Rh incompatibility
• anoxia
• hyperbilirubinemia
• birth trauma (hemorrhage into inner ear)

Postnatal
• meningitis, mumps, measles

High Risk Factors (for hearing loss in newborns)
• low birth weight/prematurity
• perinatal anoxia (low APGARs)
• kernicterus: bilirubin >25 mg/dL
• craniofacial abnormality
• family history of deafness in childhood
• 1st trimester illness: TORCH infections
• neonatal sepsis
• ototoxic drugs
• perinatal infection, including post-natal meningitis
• consanguinity
• 50-75% of newborns with SNHL have at least one of the above risk factors and 90% of these have spent time in the NICU
• presence of any risk factor: ABR study performed before leaving NICU and at 3 mo adjusted age
• early rehabilitation improves speech and school performance

Presbycusis

Definition
• SNHL associated with aging (starting in 5th and 6th decades)

Etiology
• hair cell degeneration
• age related degeneration of basilar membrane, possibly genetic etiology
• cochlear neuron damage
• ischemia of inner ear

Clinical Features
• progressive, bilateral hearing loss initially at high frequencies, then middle frequencies
• loss of discrimination of speech especially with background noise present – patients describe people as mumbling
• recruitment phenomenon: inability to tolerate loud sounds
• tinnitus

Treatment
• hearing aid if patient has difficulty functioning, hearing loss >30-35 dB, and good speech discrimination
• ± lip reading, auditory training, auditory aids (doorbell and phone lights)

Sudden Sensorineural Hearing Loss

Clinical Features
• presents as a sudden onset of significant SNHL (usually unilateral) ± tinnitus, aural fullness
• usually idiopathic, rule out other causes
  ▪ autoimmune causes (e.g. ESR, rheumatoid factor, ANA)
  ▪ MRI to rule out tumour and/or CT to rule out ischemic/hemorrhagic stroke if associated with any other focal neurological signs (e.g. vertigo, ataxia, abnormality of CN V or VII, weakness)

Treatment
• oral corticosteroids within 3 d of onset: prednisone 1 mg/kg/d for 10-14 d

Prognosis
• depends on degree of hearing loss
• 70% resolve within 10-14 d
• 20% experience partial resolution
• 10% experience permanent hearing loss

Autoimmune Inner Ear Disease

Etiology
• idiopathic
• may be associated with systemic autoimmune diseases (e.g. rheumatoid arthritis, SLE), vasculitides (e.g. GPA, polyarteritis nodosa), and allergies

Epidemiology
• most common between ages 20-50

Clinical Features
• rapidly progressive or fluctuating bilateral SNHL
• ± tinnitus, aural fullness, vestibular symptoms (e.g. ataxia, disequilibrium, vertigo)

Investigations
• autoimmune workup: CBC, ESR, ANA, rheumatoid factor

Presbycusis is the most common cause of SNHL

Sudden SNHL may easily be confused with ischemic brain events. It is important to keep a high index of suspicion especially with elderly patients presenting with sudden SNHL as well as vertigo
Treatment
- high-dose corticosteroids: treat early for at least 30 d
- consider cytotoxic medication for steroid non-responders

Drug Ototoxicity

Aminoglycosides
- streptomycin and gentamicin (vestibulotoxic), kanamycin, and tobramycin (cochleotoxic)
- toxic to hair cells by any route: oral, IV, and topical (if the TM is perforated)
- destroys sensory hair cells: outer first, inner second (therefore otoacoustic emissions are lost first)
- high frequency hearing loss develops earliest
- ototoxicity occurs days to weeks post-treatment
- must monitor with peak and trough levels when prescribed, especially if patient has neutropenia and/or history of ear or renal problems
- q24h dosing recommended (with amount determined by creatinine clearance)
- aminoglycoside toxicity displays saturable kinetics, therefore, once daily dosing presents less risk than divided daily doses
- duration of treatment is the most important predictor of ototoxicity
- treatment: immediately stop aminoglycosides

Salicylates
- hearing loss with tinnitus, reversible if discontinued

Antimalarials (Quinines)
- hearing loss with tinnitus
- reversible if discontinued but can lead to permanent loss

Others
- many antineoplastic agents are ototoxic (weigh risks vs. benefits)
- loop diuretics

Noise-Induced Sensorineural Hearing Loss

Pathogenesis
- 85-90 dB over months or years or single sound impulses >135 dB can cause cochlear damage
- bilateral SNHL initially and most prominently at 4000 Hz (resonant frequency of the temporal bone), known as “boilermaker’s notch” on audiogram, extends to higher and lower frequencies with time (see Figure 16D, OT10)
- speech reception not altered until hearing loss >30 dB at speech frequency, therefore considerable damage may occur before patient complains of hearing loss
- difficulty with speech discrimination, especially in situations with competing noise

Phases of Hearing Loss
- dependent on: intensity of sound and duration of exposure
- temporary threshold shift
  ▪ when exposed to loud sound, decreased sensitivity or increased threshold for sound
  ▪ may have associated aural fullness and tinnitus
  ▪ with removal of noise, hearing returns to normal
- permanent threshold shift
  ▪ hearing does not return to previous state

Treatment
- hearing aid
- prevention
  ▪ ear protectors: muffs, plugs
  ▪ limit exposure to noise with frequent rest periods
  ▪ regular audiologic follow-up
Temporal Bone Fractures

Table 9. Features of Temporal Bone Fractures

<table>
<thead>
<tr>
<th></th>
<th>Transverse (1)</th>
<th>Longitudinal (2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extension</td>
<td>Into bony labyrinth and internal auditory meatus</td>
<td>Into middle ear</td>
</tr>
<tr>
<td>Incidence</td>
<td>10-20%</td>
<td>70-90%</td>
</tr>
<tr>
<td>Etiology</td>
<td>Frontal/occipital trauma</td>
<td>Lateral skull trauma</td>
</tr>
<tr>
<td>CN Pathology</td>
<td>CN VII palsy (50%)</td>
<td>CN VII palsy (10-20%)</td>
</tr>
<tr>
<td>Hearing Loss</td>
<td>SNHL due to direct cochlear injury</td>
<td>CHL secondary to ossicular injury</td>
</tr>
<tr>
<td>Vestibular Symptoms</td>
<td>Sudden onset vestibular symptoms due to direct semicircular canal injury (vertigo, spontaneous nystagmus)</td>
<td>Rare</td>
</tr>
<tr>
<td>Other Features</td>
<td>Intact external auditory meatus, TM ± hemotympanum</td>
<td>Tom TM or hemotympanum</td>
</tr>
<tr>
<td></td>
<td>Spontaneous nystagmus</td>
<td>Bleeding from external auditory canal</td>
</tr>
<tr>
<td></td>
<td>CSF leak in Eustachian tube to nasopharynx ± rhinorrhea</td>
<td>CSF otorrhea</td>
</tr>
<tr>
<td></td>
<td>(risk of meningitis)</td>
<td>Battle’s sign = mastoid ecchymoses</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Raccoon eyes = periorbital ecchymoses</td>
</tr>
</tbody>
</table>

- characterized as longitudinal or transverse relative to the long axis of the petrous temporal bone
- temporal bone fractures are rarely purely transverse or longitudinal (often a mixed picture)

Diagnosis
- otoscopy
- do not syringe or manipulate external auditory meatus due to risk of inducing meningitis via TM perforation
- CT head
- audiology, facial nerve tests (for transverse fractures), Schirmer’s test (of lacrimation), stapedial reflexes if CN VII palsy
- if suspecting CSF leak: look for halo sign, send fluid for β-2 transferrin

Treatment
- ABCs
- medical: expectant, prevent otogenic meningitis
- surgical: explore temporal bone, indications
  - CN VII palsy (immediate and complete)
  - gunshot wound
  - depressed fracture of external auditory meatus
  - early meningitis (mastoidectomy)
  - bleeding intracranially from sinus
  - CSF otorrhea (may resolve spontaneously)

Complications
- AOM ± labyrinthitis ± mastoiditis
- meningitis/epidural abscess/brain abscess
- post-traumatic cholesteatoma

Facial Nerve (CN VII) Paralysis

Etiology
- supranuclear and nuclear (MS, poliomyelitis, cerebral tumours)
- infranuclear

Treatment
- treat according to etiology plus provide corneal protection with artificial tears, nocturnal lid taping, tarsorrhaphy, gold weighting of upper lid
- facial paralysis that does not resolve with time or with medical treatment will often be referred for possible reanimation techniques to restore function
  - common reanimation techniques include
    - direct facial nerve anastomosis
    - interpositional grafts
    - anastomosis to other motor nerves
    - muscle transpositions
Table 10. Differential Diagnosis of Peripheral Facial Paralysis (PFP)

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Incidence</th>
<th>Findings</th>
<th>Investigations</th>
<th>Treatment, Follow-up, and Prognosis (Px)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell’s Palsy</td>
<td>80-90% of PFP</td>
<td>Hx: Acute onset, numbness of ear, Schirmer’s test, Schlag’s test, hyperacusis (30%)</td>
<td>Stapedial reflex absent, audiometry normal, EMG – best measure for prognosis, topographic testing, MRI with gadolinium – enhancement of CN VII and VIII</td>
<td>Rx: Protect the eye to prevent exposure keratitis with patching or tarsorrhaphy, systemic steroids may lessen degeneration and hasten recovery, consider antiviral (acyclovir)</td>
</tr>
<tr>
<td>Ramsay Hunt Syndrome (Herpes Zoster Oticus)</td>
<td>4.5-9% of PFP</td>
<td>Hx: Hyperacusis, SNHL, severe pain of pinna, mouth, or face</td>
<td>Stapedial reflex absent, audiometry – SNHL, viral ELISA studies to confirm MRI with gadolinium – enhancement of 86% of facial nerves</td>
<td>Rx: Avoid touching lesions to prevent spread of infection, systemic steroids can relieve pain, vertigo, avoid postherpetic neuralgia, acyclovir may lessen pain, aid healing of vesicles</td>
</tr>
<tr>
<td>TEMPORAL BONE FRACTURE</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Longitudinal (90%)</td>
<td>20% have PFP</td>
<td>Hx: Blow to side of head, trauma to side of head, neuro findings consistent with epidural/subdural bleed</td>
<td>Skull x-rays, CT head</td>
<td>Injuy usually due to stretch or impingement; may recover with time</td>
</tr>
<tr>
<td>Transverse (10%)</td>
<td>40% have PFP</td>
<td>Hx: Blow to frontal or occipital area, trauma to front or back of head</td>
<td>Skull x-rays, CT head</td>
<td>Nerve transection more likely</td>
</tr>
<tr>
<td>Iatrogenic</td>
<td>Variable (depending on level of injury)</td>
<td>Wait for lidocaine to wear off EMG</td>
<td>Rx: Exploration if complete nerve paralysis, no exploration if any movement present</td>
<td></td>
</tr>
</tbody>
</table>

Source: Paul Warrick, MD

Rhinitis

Definition
- inflammation of the lining (mucosa) of the nasal cavity

Table 11. Classification of Rhinitis

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Non-Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perennial non-allergic</td>
<td>Rhinitis medicamentosa</td>
</tr>
<tr>
<td>Asthma, ASA sensitivity</td>
<td>Topical decongestants</td>
</tr>
<tr>
<td>Allergic</td>
<td>Hormonal</td>
</tr>
<tr>
<td>Seasonal</td>
<td>Pregnancy</td>
</tr>
<tr>
<td>Perennial</td>
<td>Estrogens</td>
</tr>
<tr>
<td>Atrophic</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Acquired: Klebsiella ozena (especially in elderly)</td>
<td>Idiopathic vasomotor</td>
</tr>
<tr>
<td>Acquired: post-surgery if too much mucosa or turbinate has been resected</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Infectious</td>
</tr>
<tr>
<td>Viral: e.g. rhinovirus, influenza, parainfluenza, etc.</td>
<td>Viral: e.g. S. aureus</td>
</tr>
<tr>
<td>Bacterial: e.g. S. aureus</td>
<td>Fungal</td>
</tr>
<tr>
<td></td>
<td>Granulomatosus: TB, syphilis, leprosy</td>
</tr>
<tr>
<td>Non-infectious</td>
<td>Non-infectious</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>GPA</td>
<td>GPA</td>
</tr>
<tr>
<td>Irritant</td>
<td>Irritant</td>
</tr>
<tr>
<td>Dust</td>
<td>Dust</td>
</tr>
<tr>
<td>Chemicals</td>
<td>Chemicals</td>
</tr>
<tr>
<td>Pollution</td>
<td>Pollution</td>
</tr>
</tbody>
</table>

Rhinitis medicamentosa: rebound congestion due to the overuse of intranasal vasoconstrictors; for prevention, use of these medications for only 5-7 d is recommended
### Table 12. Nasal Discharge: Character and Associated Conditions

<table>
<thead>
<tr>
<th>Character</th>
<th>Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watery/mucoid</td>
<td>Allergic, viral, vasomotor, CSF leak (halo sign)</td>
</tr>
<tr>
<td>Mucopurulent</td>
<td>Bacterial, foreign body</td>
</tr>
<tr>
<td>Serosanguinous</td>
<td>Neoplasia</td>
</tr>
<tr>
<td>Bloody</td>
<td>Trauma, neoplasia, bleeding disorder, hypertension/vascular disease</td>
</tr>
</tbody>
</table>

### Allergic Rhinitis (Hay Fever)

#### Definition
- rhinitis characterized by an IgE-mediated hypersensitivity to foreign allergens
- acute-and-seasonal or chronic-and-perennial
- perennial allergic rhinitis often confused with recurrent colds

#### Etiology
- when allergens contact the respiratory mucosa, specific IgE antibody is produced in susceptible hosts
- concentration of allergen in the ambient air correlates directly with the rhinitis symptoms

#### Epidemiology
- age at onset usually <20 yr
- more common in those with a personal or family history of allergies/atopy

#### Clinical Features
- nasal: obstruction with pruritus, sneezing
- clear rhinorrhea (containing increased eosinophils)
- itching of eyes with tearing
- frontal headache and pressure
- mucosa: swollen, pale, "boggy"
- seasonal (summer, spring, early autumn)
  - pollens from trees
  - lasts several weeks, disappears, and recurs following year at same time
- perennial
  - inhaled: house dust, wool, feathers, foods, tobacco, hair, mould
  - ingested: wheat, eggs, milk, nuts
  - occurs intermittently for years with no pattern or may be constantly present

#### Complications
- chronic sinusitis/polyps
- serous otitis media

#### Diagnosis
- history
- direct exam
- allergy testing

#### Treatment
- education: identification and avoidance of allergen
- nasal irrigation with saline
- antihistamines (e.g. diphenhydramine, fexofenadine)
- oral decongestants (e.g. pseudoephedrine, phenylpropanolamine)
- topical decongestant (may lead to rhinitis medicamentosa)
- other topicals: steroids (fluticasone), disodium cromoglycate, antihistamines, ipratropium bromide
- oral steroids if severe
- desensitization by allergen immunotherapy

Congestion reduces nasal airflow and allows the nose to repair itself (i.e. washes away the irritants) Treatment should focus on the initial insult rather than target this defense mechanism
Vasomotor Rhinitis

- neurovascular disorder of nasal parasympathetic system (vidian nerve) affecting mucosal blood vessels
- nonspecific reflex hypersensitivity of nasal mucosa
- caused by
  - temperature change
  - alcohol, dust, smoke
  - stress, anxiety, neurosis
  - endocrine: hypothyroidism, pregnancy, menopause
  - parasympathomimetic drugs
  - beware of rhinitis medicamentosa: reactive vasodilation due to prolonged use (>5 d) of nasal drops and sprays (Dristan*, Otrivin*)

Clinical Features
- chronic intermittent nasal obstruction, varies from side to side
- rhinorrhea: thin, watery
- mucosa and turbinates: swollen
- nasal allergy must be ruled out

Treatment
- elimination of irritant factors
- parasympathetic blocker (Atrovent* nasal spray)
- steroids (e.g. beclomethasone, fluticasone)
- surgery (often of limited lasting benefit): electrocautery, cryosurgery, laser treatment, or removal of inferior or middle turbinates
- vidian neurectomy (rarely done)
- symptomatic relief with exercise (increased sympathetic tone)

Rhinosinusitis

Pathogenesis of Rhinosinusitis
- ostial obstruction or dysfunctional cilia permit stagnant mucous and, consequently, infection
- all sinuses drain to a common prechamber under the middle meatus called the osteomeatal complex

Definition
- inflammation of the mucosal lining of the sinuses and nasal passages

Classification
- acute: <4 wk
- subacute: 4-8 wk
- chronic: >8-12 wk

Table 13. Etiologies of Rhinosinusitis

<table>
<thead>
<tr>
<th>Ostial Obstruction</th>
<th>Inflammation</th>
<th>Systemic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mechanical</td>
<td>Septal deviation</td>
<td>Cystic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Turbinate hypertrophy</td>
<td>Immotile cilia (e.g. Kartagener’s)</td>
</tr>
<tr>
<td></td>
<td>Polyps</td>
<td>Dental</td>
</tr>
<tr>
<td></td>
<td>Tumours</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Adenoid hypertrophy</td>
<td>Infection</td>
</tr>
<tr>
<td></td>
<td>Foreign body</td>
<td>Facial fractures</td>
</tr>
<tr>
<td></td>
<td>Congenital abnormalities (e.g. cleft palate)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>GPA</td>
<td></td>
</tr>
</tbody>
</table>
Acute Bacterial Rhinosinusitis

Definition
- bacterial infection of the paranasal sinuses and nasal passages lasting >7 d
- clinical diagnosis requiring ≥ 2 major symptoms, at least one of the symptoms is either nasal obstruction or purulent/discoloured nasal discharge

- **major symptoms**
  - facial pain/pressure/fullness
  - nasal obstruction
  - purulent/discoloured nasal discharge
  - hyposmia/anosmia

- **minor symptoms**
  - headache
  - halitosis
  - fatigue
  - dental pain
  - cough
  - ear pain/fullness

Etiology
- bacteria: *S. pneumoniae* (35%), *H. influenzae* (35%), *M. catarrhalis*, *S. aureus*, anaerobes (dental)
- children are more prone to a bacterial etiology, but viral is still more common
- maxillary sinus most commonly affected
- must rule out fungal causes (mucormycosis) in immunocompromised hosts (especially if painless, black or pale mucosa on examination)

Clinical Features
- sudden onset of
  - nasal blockage/congestion and/or purulent nasal discharge/posterior nasal drip
  - ± facial pain or pressure, hyposmia, sore throat
- persistent/worsening symptoms >5-7 d or presence of purulence for 3-4 d with high fever
- speculum exam: erythematous mucosa, mucopurulent discharge, pus originating from the middle meatus
- predisposing factors: viral URTI, allergy, dental disease, anatomical defects
- differentiate from acute viral rhinosinusitis (course: <10 d, peaks by 3 d)

Management
- depends on symptom severity (i.e. intensity/duration of symptoms, impact on quality of life)
- mild-moderate: INCS
- if no response within 72 h, add antibiotics
- severe: INCS + antibiotics
- antibiotics
  - 1st line: amoxicillin x 10 d (TMP-SMX or macrolide if penicillin allergy)
  - if no response to 1st line antibiotics within 72 h, switch to 2nd line
  - 2nd line: fluoroquinolones or amoxicillin-clavulanic acid inhibitors
  - adjuvant therapy (saline irrigation, analgesics, oral/topical decongestant) may provide symptomatic relief
- CT indicated only if complications are suspected

Chronic Rhinosinusitis

Definition
- inflammation of the mucosa of paranasal sinuses and nasal passages >8-12 wk
- diagnosis requiring ≥ 2 major symptoms for >8-12 wk and ≥ 1 objective finding of inflammation of the paranasal sinuses (CT/endoscopy)

Etiology
- unclear etiology but the following may contribute or predispose
  - inadequate treatment of acute rhinosinusitis
  - bacterial colonization/biofilms
    - *S. aureus*, enterobacteriaceae, *Pseudomonas*, *S. pneumoniae*, *H. influenzae*, β-hemolytic streptococci
  - fungal infection (e.g. *Aspergillus*, *Zygomycetes*, *Candida*)
  - anatomic abnormality (e.g. lost ostia patency, deviated septum – predisposing factors)
  - allergy/allergic rhinitis
  - ciliary disorder (e.g. cystic fibrosis, Kartagener syndrome)
  - chronic inflammatory disorder (e.g. GPA)
  - untreated dental disease

Acute Rhinosinusitis Complications
Consider hospitalization if any of the following are suspected
- • Orbital (Chandler’s classification)
  - Periorbital cellulitis
  - Orbital cellulitis
  - Subperiosteal abscess
  - Orbital abscess
  - Cavernous sinus thrombosis
- • Intracranial
  - Meningitis
  - Abscess
  - Bony
    - Subperiosteal frontal bone abscess (“Pott’s Puffy tumour”)
    - Osteomyelitis
  - Neurologic
    - Superior orbital fissure syndrome (CN III/IV/VI palsy, immobile globe, dilated pupils, ptosis, V1 hypoesthesia)
    - Orbital apex syndrome (as above, plus neuritis, papilledema, decreased visual acuity)
Clinical Features (similar to acute, but less severe)
- chronic nasal obstruction
- purulent anterior/posterior nasal discharge
- facial congestion/fullness
- facial pain/pressure
- hyposmia/anosmia
- halitosis
- chronic cough
- maxillary dental pain

Management
- identify and address contributing or predisposing factors
- obtain CT or perform endoscopy
- if polyps present: INCS, oral steroids ± antibiotics (if signs of infection), refer to otolaryngologist/H&N surgeon
- if polyps absent: INCS, antibiotics, saline irrigation, oral steroids (severe cases)
- antibiotics for 3-6 wk
  - amoxillin-clavulanic acid inhibitors, fluoroquinolone (moxifloxacin), macrolide (clarithromycin), clindamycin, Flagyl® (metronidazole)
- surgery if medical therapy fails or fungal sinusitis: FESS, balloon sinoplasty

Complications
- same as acute sinusitis, mucocele

Epistaxis

Blood Supply to the Nasal Septum (see Figure 4, OT3)
1. Superior posterior septum
   - internal carotid → ophthalmic → anterior/posterior ethmoidal
2. Posterior septum
   - external carotid → internal maxillary → sphenopalatine artery → nasopalatine
3. Lower anterior septum
   - external carotid → facial artery → superior labial artery → nasal branch
   - external carotid → internal maxillary → descending palatine → greater palatine
- these arteries all anastomose to form Kiesselbach’s plexus, located at Little’s area (anterior-inferior portion of the cartilaginous septum)
- bleeding from above middle turbinate is internal carotid, and from below is external carotid

Table 14. Etiology of Epistaxis

<table>
<thead>
<tr>
<th>Type</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>Trauma (most common)</td>
</tr>
<tr>
<td></td>
<td>• Fractures: facial, nasal</td>
</tr>
<tr>
<td></td>
<td>• Self-induced: digital, foreign body</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic: nasal, sinus, orbit surgery</td>
</tr>
<tr>
<td></td>
<td>Barometric changes</td>
</tr>
<tr>
<td></td>
<td>Nasal dryness: dry air ± septal deformities</td>
</tr>
<tr>
<td></td>
<td>Septal perforation</td>
</tr>
<tr>
<td></td>
<td>Chemical: cocaine, nasal sprays, ammonia, etc.</td>
</tr>
<tr>
<td></td>
<td>Tumours</td>
</tr>
<tr>
<td></td>
<td>• Benign: polyps, inverting papilloma, angiofibroma</td>
</tr>
<tr>
<td></td>
<td>• Malignant: SCC, esthesioneuroblastoma (olfactory neuroblastoma)</td>
</tr>
<tr>
<td></td>
<td>Inflammation</td>
</tr>
<tr>
<td></td>
<td>• Rhinitis: allergic, non-allergic</td>
</tr>
<tr>
<td></td>
<td>• Infections: bacterial, viral, fungal</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Systemic</td>
<td>Coagulopathies</td>
</tr>
<tr>
<td></td>
<td>• Meds: anticoagulants, NSAIDs</td>
</tr>
<tr>
<td></td>
<td>• Hemophilias, von Willebrand’s</td>
</tr>
<tr>
<td></td>
<td>• Hematological malignancies</td>
</tr>
<tr>
<td></td>
<td>• Liver failure, uremia</td>
</tr>
<tr>
<td></td>
<td>Vascular: HTN, atherosclerosis, Osler-Weber-REndu (hereditary hemorrhagic telangiectasia)</td>
</tr>
<tr>
<td></td>
<td>Others: GPA, SLE</td>
</tr>
</tbody>
</table>

Investigations
- CBC, PT/PTT (if indicated)
- x-ray, CT as needed

Treatment
- locate bleeding and achieve hemostasis
1. ABCs
- lean patient forward to minimize swallowing blood and avoid airway obstruction
- apply constant firm pressure for 20 min on cartilaginous part of nose (not bony pyramid)
- if significant bleeding, assess vitals for signs of hemorrhagic shock ± IV NS, cross-match blood

2. Determine Site of Bleeding
- anterior/posterior hemorrhage defined by location in relationship to bony septum
- visualize nasal cavity with speculum
- use cotton pledget with topical lidocaine ± topical decongestant (i.e. Otrivin®) to help identify area of bleeding (often anterior septum)
- if suspicious bleeding disorder, coagulation workup (platelet number and platelet function assay)

3. Control the Bleeding
- first line topical vasoconstrictors (Otrivin®)
- if first line fails and bleeding adequately visualized, cauterize with silver nitrate
- do not cauterize both sides of the septum at one time due to risk of septal perforation from loss of septal blood supply

A. Anterior hemorrhage treatment
- if failure to achieve hemostasis with cauterization
- place anterior pack* with half inch Vaseline®-soaked ribbon gauze strips layered from nasal floor toward nasal roof extending to posterior choanae or lubricated absorbable packing (i.e. Gelfoam wrapped in Surgicel®) for 2-3 d
- can also attempt packing with Merocel® or nasal tampons of different shapes
- can also apply Floseal® (hemostatic matrix consisting of topical human thrombin and cross-linked gelatin) if other methods fail

B. Posterior hemorrhage treatment
- if unable to visualize bleeding source, then usually posterior source
- place posterior pack* using a Foley catheter, gauze pack, or Epistat® balloon
- subsequently, layer anterior packing bilaterally
- admit to hospital with packs in for 3-5 d
- watch for complications: hypoxemia (nasopulmonic reflex), toxic shock syndrome (Rx: remove packs immediately), pharyngeal fibrosis/stenosis, alar/septal necrosis, aspiration

C. If anterior/posterior packs fail to control epistaxis
- ligation or embolization of culprit arterial supply by interventional radiology
- ± septoplasty
- * antibiotics for any posterior pack or any pack left for >48 h because of risk of toxic shock syndrome

4. Prevention
- prevent drying of nasal mucosa with humidifiers, saline spray, or topical ointments
- avoidance of irritants
- medical management of HTN and coagulopathies

---

**Hoarseness**

Definitions
- hoarseness: change in voice quality, ranging from voice harshness to voice weakness; reflects abnormalities anywhere along the vocal tract from oral cavity to lungs
- dysphonia: a general alteration in voice quality
- aphasis: no sound emanates from vocal folds

**Acute Laryngitis**

Definition
- <2 wk inflammatory changes in laryngeal mucosa

Etiology
- viral: influenza, adenovirus
- bacterial: Group A Streptococcus
- mechanical acute voice strain → submucosal hemorrhage → vocal cord edema → hoarseness
- environmental: toxic fume inhalation

Clinical Features
- URTI symptoms, hoarseness, aphasis, cough attacks, ± dyspnea
- true vocal cords erythematous/edematous with vascular injection and normal mobility

Treatment
- usually self-limited, resolves within ~1 wk
- voice rest
- humidification
- hydration

If hoarseness present for >2 wk in a smoker, laryngoscopy must be done to rule out malignancy

Vocal Cord Paralysis

Unilateral: affected cord lies in the parmedian position, inadequate glottic closure during phonation → weak, breathy voice. Usually mediates with time whereby phonation and aspiration improve. Treatment options include voice therapy, injection laryngoplasty (Radiesse), medialization using silastic block

Bilateral: cords rest in midline therefore voice remains good but respiratory function is compromised and may present as stridor. If no respiratory issues, may monitor closely and wait for improvement. If respiratory issues, intubate and will likely require a tracheotomy
• avoid irritants (e.g. smoking)
• treat with antibiotics if there is evidence of coexistent bacterial pharyngitis

### Chronic Laryngitis

**Definition**
• >2 wk inflammatory changes in laryngeal mucosa

**Etiology**
• repeated attacks of acute laryngitis
• chronic irritants (dust, smoke, chemical fumes)
• chronic voice strain
• chronic rhinosinusitis with postnasal drip
• chronic EtOH use
• esophageal disorders: GERD, Zenker’s diverticulum, hiatus hernia
• systemic: allergy, hypothyroidism, Addison's disease

**Clinical Features**
• chronic dysphonia: rule out malignancy
• cough, globus sensation, frequent throat clearing 2º to GERD
• laryngoscopy: cords erythematous, thickened with ulceration/granuloma formation, and normal mobility

**Treatment**
• remove offending irritants
• treat related disorders (e.g. antisecretory therapy for GERD)
• speech therapy with voice rest
• ± antibiotics ± steroids to decrease inflammation
• laryngoscopy to rule out malignancy

### Vocal Cord Polyps

**Definition**
• structural manifestation of vocal cord irritation
• acutely, polyp forms 2º to capillary damage in the subepithelial space during extreme voice exertion

**Etiology**
• most common benign tumour of vocal cords
• voice strain (muscle tension dysphonia)
• laryngeal irritants (GERD, allergies, tobacco)

**Epidemiology**
• 30-50 yr of age
• M>F

**Clinical Features**
• hoarseness, aphonia, cough attacks ± dyspnea
• pedicled or sessile polyp on free edge of vocal cord
• typically polyp asymmetrical, soft, and smooth
• more common on the anterior 1/3 of the vocal cord
• intermittent respiratory distress with large polyps

**Treatment**
• avoid irritants
• endoscopic laryngeal microsurgical removal if persistent or if high risk of malignancy

### Vocal Cord Nodules

**Definition**
• vocal cord callus
• i.e. “screamer’s or singer’s nodules”

**Etiology**
• early nodules occur 2º to submucosal hemorrhage
• mature nodules result from hyalinization which occurs with long-term voice abuse
• chronic voice strain
• frequent URTI, smoke, EtOH

---

**Vocal Cords: Polyps vs. Nodules**

<table>
<thead>
<tr>
<th>Polyps</th>
<th>Nodule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral, asymmetric</td>
<td>Bilateral</td>
</tr>
<tr>
<td>Acute onset</td>
<td>Gradual onset</td>
</tr>
<tr>
<td>May resolve spontaneously</td>
<td>Often follow a chronic course</td>
</tr>
<tr>
<td>Subepithelial capillary breakage</td>
<td>Acute: submucosal hemorrhage or edema</td>
</tr>
<tr>
<td>Chronically: hyalinization within submucosal lesion</td>
<td></td>
</tr>
<tr>
<td>Soft, smooth, fusiform, pedunculated mass</td>
<td>Acute: small, discrete nodules</td>
</tr>
<tr>
<td>Chronic: hard, white, thickened fibrosed nodules</td>
<td></td>
</tr>
<tr>
<td>Proton pump inhibitor</td>
<td>Voice rest but no whispering, hydration, speech therapy if refractory to therapy</td>
</tr>
<tr>
<td>Surgical excision if persistent or in presence of risk factors for laryngeal cancer</td>
<td>Surgical excision as last resort</td>
</tr>
</tbody>
</table>
Epidemiology
- frequently in singers, children, bartenders, and school teachers
- F>M

Clinical Features
- hoarseness worst at end of day
- on laryngoscopy
  - often bilateral
  - at the junction of the anterior 1/3 and posterior 2/3 of the vocal cords – point of maximal cord vibration
- chronic nodules may become fibrotic, hard, and white

Treatment
- voice rest
- hydration
- speech therapy
- avoid irritants
- surgery rarely indicated for refractory nodules

Benign Laryngeal Papillomas

Etiology
- HPV types 6, 11
- possible hormonal influence, possibly acquired during delivery

Epidemiology
- biphasic distribution: 1) birth to puberty (most common laryngeal tumour) and 2) adulthood

Clinical Features
- hoarseness and airway obstruction
- can seed into tracheobronchial tree
- highly resistant to complete removal
- some juvenile papillomas resolve spontaneously at puberty
- may undergo malignant transformation
- laryngoscopy shows wart-like lesions in supraglottic larynx and trachea

Treatment
- microdebridement or CO₂ laser
- adjuvants under investigation: interferon, cidofovir, acyclovir
- HPV vaccine may prevent/decrease the incidence but more research is needed

Laryngeal Carcinoma

- see Neoplasms of the Head and Neck, OT35

Salivary Glands

Sialadenitis

Definition
- inflammation of salivary glands

Etiology
- viral most common (mumps)
- bacterial causes: S. aureus, S. pneumoniae, H. influenzae
- obstructive vs. non-obstructive
- obstructive infection involves salivary stasis and bacterial retrograde flow

Predisposing Factors
- HIV
- anorexia/bulimia
- Sjögren's syndrome
- Cushing's, hypothyroidism, DM
- hepatic/renal failure
- meds that increase stasis: diuretics, TCAs, β-blockers, anticholinergics, antibiotics
- sialolithiasis (can cause chronic sialadenitis)
Clinical Features
- acute onset of pain and edema of parotid or submandibular gland that may lead to marked swelling
- ± fever
- ± leukocytosis
- ± suppurative drainage from punctum of the gland

Investigations
- U/S imaging to differentiate obstructive vs. non-obstructive sialadenitis

Treatment
- bacterial: treat with cloxacillin ± abscess drainage, sialogogues
- viral: no treatment

Sialolithiasis

Definition
- ductal stone (mainly hydroxyapatite) in adults, sand/sludge in children, leading to chronic sialadenitis
- 80% in submandibular gland, <20% in parotid gland, ~1% in sublingual gland

Risk Factors
- any condition causing duct stenosis or a change in salivary secretions (e.g. dehydration, diabetes, EtOH, hypercalcemia, psychiatric medication)

Clinical Features
- pain and tenderness over involved gland
- intermittent swelling related to meals
- digital palpation reveals presence of calculus

Investigations
- U/S ± sialogram

Treatment
- may resolve spontaneously
- encourage salivation to clear calculus
- massage, analgesia, antibiotics, sialogogues (e.g. lemon wedges, sour lemon candies), warm compresses
- remove calculi endoscopically, by dilating duct or orifice, or by excision through floor of the mouth
- if calculus is within the gland parenchyma, the whole gland must be excised

Salivary Gland Neoplasms

Etiology
- anatomic distribution
  - parotid gland: 70-85%
  - submandibular gland: 8-15%
  - sublingual gland: 1%
  - minor salivary glands, most concentrated in hard palate: 5-8%
- malignant (see Table 15, OT32 and Table 16, OT36)
- benign
  - benign mixed (pleomorphic adenoma): 80%
  - Warthin's tumour (5-10% bilateral, M>F): 10%
  - cysts, lymph nodes and adenomas: 10%
  - oncocytoma: <1%

Epidemiology
- 3-6% of all head and neck neoplasms in adults
- mean age at presentation: 55-65
- M=F
**Parotid Gland Neoplasms**

**Clinical Features**
- 80% benign (pleomorphic adenoma: most common), 20% malignant (mucoepidermoid: most common)
- if bilateral, suggests benign process (Warthin's tumour, Sjögren's, bulimia, mumps) or possible lymphoma
- facial nerve involvement (i.e. facial paralysis): increases risk of malignancy

**Investigations**
- FNA biopsy
- CT, U/S, or MRI to determine extent of tumour

**Treatment**
- treatment of choice is surgery for all salivary gland neoplasms – benign and malignant
  - pleomorphic adenomas are excised due to risk of malignant transformation (5% risk over prolonged period of time)
  - superficial tumour
    - superficial parotidectomy above plane of CN VII ± radiation
  - incisional biopsy contraindicated
  - deep lesion
    - near-total parotidectomy sparing as much of CN VII as possible
    - if CN VII involved then it is removed and cable grafted
  - complications of parotid surgery
    - haematoma, infection, salivary fistula, temporary facial paresis, Frey’s syndrome (gustatory sweating)

**Prognosis**
- benign: excellent, <5% of pleomorphic adenomas may recur
- malignant: dependent on stage and type of malignancy (see Table 16, OT36)

**Neck Masses**

**Approach to a Neck Mass**
- ensure that the neck mass is not a normal neck structure (hyoid, transverse process of C1 vertebra, prominent carotid bulb)
- any neck mass persisting for >2 wk should be investigated for possible neoplastic causes

**Table 15. Acquired Causes of Neck Lumps According to Age**

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Possible Causes of Neck Lump</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>1. Inflammatory 2. Congenital 3. Neoplastic</td>
</tr>
<tr>
<td>&gt;40</td>
<td>1. Neoplastic 2. Inflammatory 3. Congenital</td>
</tr>
</tbody>
</table>

**Differential Diagnosis**
- congenital
  - lateral (branchial cleft cyst, lymphatic/venous/venolymphatic malformation)
  - midline (thyroglossal duct cyst, dermoid cyst, laryngocele)
- infectious/inflammatory
  - reactive lymphadenopathy (2nd to tonsillitis, pharyngitis)
  - infectious mononucleosis
  - Kawasaki, Kikuchi, Kimura, Cat Scratch, Castleman’s
  - HIV
  - salivary gland calculi, sialadenitis
- thyroiditis
- granulomatous disease
- mycobacterial infections
- sarcoidosis
- neoplastic
  - lymphoma
  - salivary gland tumours
  - thyroid tumours
  - metastatic malignancy (“unknown primary”)

**DDx Parotid Tumour**

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleomorphic adenoma</td>
<td>Mucoepidermoid carcinoma</td>
</tr>
<tr>
<td>Warthin’s tumour (more common in men)</td>
<td>Salivary gland tumours</td>
</tr>
<tr>
<td>Benign lymphoepithelial cysts (viral etiology e.g. HIV)</td>
<td>Thyroid tumours</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>Metastatic malignancy (“unknown primary”)</td>
</tr>
</tbody>
</table>

**Frey’s syndrome** is a post-operative complication characterized by gustatory sweating. It is due to aberrant innervation of cutaneous sweat glands by parasympathetic nerve fibres that are divided during surgery.
**Evaluation**

**Investigations**
- history and physical (including nasopharynx and larynx)
- all other investigations and imaging are dependent upon clinical suspicion following history and physical
- laboratory investigations
  - WBC: infection vs. lymphoma
  - Mantoux TB test
  - thyroid function tests and scan
- imaging
  - neck U/S
  - CT scan
  - angiography: vascularity and blood supply to mass
- biopsy: for histologic examination
  - FNA: least invasive
  - needle biopsy
  - open biopsy: for lymphoma
- identification of possible primary tumour (rule out a metastatic lymph node from an “unknown primary”)
  - panendoscopy: nasopharyngoscopy, laryngoscopy, esophagoscopy, bronchoscopy with washings, and biopsy of suspicious lesions
  - biopsy of normal tissue of nasopharynx, tonsils, base of tongue, and hypopharynx
  - primary identified 95% of time → stage and treat
  - primary occult 5% of time: excisional biopsy of node for histologic diagnosis → manage with radiotherapy and/or neck dissection (squamous cell carcinoma)

**Congenital Neck Masses**

**Branchial Cleft Cysts/Fistula**

**Embryology**
- at the 6th wk of development, the 2nd branchial arch grows over the 3rd and 4th arches and fuses with the neighbouring caudal pre-cardial swelling forming the cervical sinus
- 3 types of malformations
  1. branchial fistula: persistent communication between skin and GI tract
  2. branchial sinus: blind-ended tract opening to skin
  3. branchial cyst: persistent cervical sinus with no external opening

**Clinical Features**
- 2nd branchial cleft malformations most common
  - sinuses and fistulae present in infancy as a small opening anterior to the sternocleidomastoid muscle
  - cysts present as a smooth, painless, slowly enlarging lateral neck mass, often following a URTI
- 1st branchial cleft malformations present as sinus/fistula or cyst in preauricular area or on face over angle of mandible
- 3rd branchial cleft malformations present as recurrent thyroiditis or thyroid abscess and have a tract leading usually to the left pyriform sinus
- there is controversy whether or not 4th branchial cleft anomalies exist, as they may be remnants of the thyrothymic axis

**Treatment**
- surgical removal of cyst or fistula tract
- if infected: allow infection to settle before removal (antibiotics may be required)
Thyroglossal Duct Cysts

Embryology
- thyroid originates as ventral midline diverticulum at base of tongue caudal to junction of 3rd and 4th branchial arches (foramen cecum) and migrates down to inferior aspect of neck
- thyroglossal duct cysts are vestigial remnants of tract

Clinical Features
- usually presents in childhood or during 20-40s as a midline cyst that enlarges with URTI and elevates with swallowing and tongue protrusion

Treatment
- pre-operative antibiotics to reduce inflammation (infection before surgery is a well described cause of recurrence)
- small potential for neoplastic transformation so complete excision of cyst and tissue around tract up to foramen cecum at base of tongue with removal of central portion of hyoid bone (Sistrunk procedure) recommended
**Lymphatic Malformation**

**Definition**
- lymphatic malformation arising from vestigial lymph channels of neck

**Clinical Features**
- usually present by age 2
- can be macrocystic (composed of large thin-walled cysts, usually below level of mylohyoid muscle) or microcystic (composed of minute cysts, usually above level of mylohyoid muscle)
- usually painless, soft, compressible
- infection causes a sudden increase in size

**Treatment**
- can regress spontaneously after bacterial infection, therefore do not plan surgical intervention until several months after infection
- macrocystic lesions can be treated by sclerotherapy or surgical excision
- microcystic lesions are difficult to treat, but can be debulked

---

**Neoplasms of the Head and Neck**

**Pre-Malignant Disease**
- **leukoplakia**
  - hyperkeratosis of oral mucosa
  - risk of malignant transformation 5-20%
- **erythroplakia**
  - red superficial patches adjacent to normal mucosa
  - commonly associated with epithelial dysplasia
  - associated with carcinoma in situ or invasive tumour in 40% of cases
- **dysplasia**
  - histopathologic presence of mitoses and prominent nucleoli
  - involvement of entire mucosal thickness = carcinoma in situ
  - associated progression to invasive cancer in 15-30% of cases

**Investigations**
- initial metastatic screen includes CXR
- scans of liver, brain, and bone only if clinically indicated
- CT scan is superior to MRI for the detection of pathologic nodal disease and bone cortex invasion
- MRI is superior to discriminate tumour from mucus and to detect bone marrow invasion
- ± PET scans

**Treatment**
- treatment depends on
  - histologic grade of tumour
  - stage
  - physical and psychological health of patient
  - facilities available
  - expertise and experience of the medical and surgical oncology team
- in general
  - 1st surgery for malignant oral cavity tumours with radiotherapy reserved for salvage or poor prognostic indicators
  - 1st radiotherapy for nasopharynx, oropharynx, hypopharynx, larynx malignancies with surgery reserved for salvage
  - palliative chemotherapy for metastatic or incurable disease
  - concomitant chemotherapy increases survival in advanced disease
  - chemotherapy has a role as induction therapy prior to surgery and radiation
  - panendoscopy to detect primary disease when lymph node metastasis is identified
  - anti-EGFR treatment (cetuximab, panitumumab) has a role as concurrent therapy with radiation for SCC of the head and neck (for advanced local and regional disease)

**Prognosis**
- synchronous tumours occur in 9-15% of patients
- late development of 2nd primary most common cause of post-treatment failure after 36 mo
### Table 16. Quick Look-Up Summary of Head and Neck Malignancies – Etiology and Epidemiology

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Epidemiology</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% SCC others: carcinoma, melanoma, minor salivary gland tumour</td>
<td>Mean age: 50-60 yr M:F Most common site of H&amp;N cancers 50% on anterior 2/3 of tongue</td>
<td>Smoking/EtOH Poor oral hygiene Leukoplakia, erythroplakia Lichen planus, chronic inflammation Sun exposure – lip HPV infection</td>
</tr>
</tbody>
</table>

| **Nose and Paranasal Sinus** | | |
| 75-80% SCC Adenocarcinoma (2nd most common) and mucosacinitumor 99% in maxillary/ethmoid sinus 10% arise from minor salivary glands | Mean age: 50-70 yr Rare tumours ↓ incidence in last 5-10 yr | Wood/shoe/textile industry Hardwood dust (nasal/ethmoid sinus) Nickel, chromium (maxillary sinus) Air pollution Chronic rhinosinusitis |

| **Carcinoma of the Pharynx – Subtypes (Nasopharynx, Oropharynx, Hypopharynx, and Larynx)** | | |
| **Nasopharynx** | | |
| 90% SCC ~10% lymphoma | Mean age: 50-59 yr M:F = 2.4:1 Incidence 0.8 per 100,000 100x increased incidence in Southern Chinese | Epstein-Barr virus (EBV) Salted fish Nickel exposure Poor oral hygiene Genetic – Southern Chinese |
| **Oropharynx** | | |
| 95% SCC – poorly differentiated Up to 70% of oropharyngeal cancer (OPC) attributable to HPV | Mean age: 50-70 yr Patients with HPV+ OPC are approximately 10 yrs younger Prevalence of HPV+ OPC has increased by 225% from 1988 to 2004. M:F = 4:1 | Smoking/EtOH HPV 16 infection: increased sexual encounters, specifically oral sex |
| **Hypopharynx** | | |
| 95% SCC 3 sites 1. pyriform sinus (60%) 2. post-cricoid (30%) 3. post pharyngeal wall (10%) | Mean age: 50-70 yr M:F 8-10% of all H&N cancer | Smoking/EtOH |
| **Larynx** | | |
| SCC most common 3 sites 1. supraglottic (30-35%) 2. glottic (60-65%) 3. subglottic (1%) | Mean age: 45-75 yr M:F = 10:1 45% of all H&N cancer | Smoking/EtOH HPV 16 infection strongly associated with the risk of laryngeal squamous cell cancers |
| **Salivary Gland** | | |
| 40% mucoepidermoid 30% adenoid cystic 5% acinic cell 5% malignant mixed 5% lymphoma | Mean age: 55-65 yr M:F 3-6% of all H&N cancer Rate of malignancy: Parotid 15-25% Submandibular 37-43% Minor salivary >80% | |
| **Thyroid (90% benign – 10% malignant)** | | |
| >80% papillary 5-15% follicular 5% medullary <5% anaplastic 1-5% hürthle cell 1-2% metastatic | Children Adults <30 or >60 yr Nodules more common in females Malignancy more common in males | Radiation exposure Family history – papillary CA or multiple endocrine neoplasia – MEN II Older age Male Papillary – Gardner’s, Cowden’s, familial adenomatous polyposis (FAP) |
| **Parathyroid** | Mean age: 44-55 yr Rare tumour | |
### Table 17. Quick Look-Up Summary of Head and Neck Malignancies – Diagnosis and Treatment

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>Investigations</th>
<th>Treatment</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Cavity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic neck mass (30%)</td>
<td>Biopsy</td>
<td>1st surgery ± neck dissection ± reconstruction</td>
<td>5 yr survival T1/T2: 75% T3/T4: 30-35% Poor prognostic indicators Depth of invasion, close surgical margins location (tongue worse than floor of mouth) Cervical nodes, extra-capsular spread</td>
</tr>
<tr>
<td>Non-healing ulcer ± bleeding</td>
<td>CT</td>
<td>± neck dissection ± reconstruction</td>
<td></td>
</tr>
<tr>
<td>Dysphagia, siaotirhea, dysphonia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral fetor, otalgia, leukoplaia, or erythroplakia (pre-malignant changes or CIS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nose and Paranasal Sinus</strong></td>
<td>CT/MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td>5 yr survival: 30-60% Poor prognosis 2° to late presentation</td>
</tr>
<tr>
<td>Early symptoms:</td>
<td>Unilateral nasal obstruction Epistaxis, rhinorrhea</td>
<td>Biopsy</td>
<td></td>
</tr>
<tr>
<td>Late symptoms:</td>
<td>2° to invasion of nose, orbit, nerves, oral cavity, skin, skull base, cribriform plate</td>
<td>CT/MRI</td>
<td></td>
</tr>
<tr>
<td><strong>Nasopharynx</strong></td>
<td>Cervical nodes (60-90%)</td>
<td>Nasopharyngoscopy Biopsy</td>
<td>1° radiation, chemoradiation Surgery for limited or recurrent disease</td>
</tr>
<tr>
<td>Nasal obstruction, epistaxis</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Unilateral otitis media ± hearing loss CN III to VI, IX to XII (25%) Proptosis, voice change, dysphagia</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Oropharynx</strong></td>
<td>Oral cavity, odynophagia</td>
<td>Pharyngoscopy Biopsy</td>
<td>1° radiation 2° surgery</td>
</tr>
<tr>
<td>Odynophagia, otalgia</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Ulecrated/enlarged tonsil</td>
<td>MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Fixed tongue/trauma/dysarthria</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Oral fetor, bloody sputum</td>
<td>MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>HPV + OPC predominantly arises at base of tongue or tonsillar region</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Cervical lymphadenopathy (60%)</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Distant mets: lung/bone/liver (7%)</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Hypopharynx</strong></td>
<td>Dysphagia, odynophagia</td>
<td>Laryngoscopy</td>
<td>1° radiation 2° surgery</td>
</tr>
<tr>
<td>Dysphagia, hoarseness</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Larynx</strong></td>
<td>Dysphagia, odynophagia, globus</td>
<td>CT</td>
<td>1° surgery 2° surgery</td>
</tr>
<tr>
<td>Dysphagia, hoarseness</td>
<td>CT</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Dyspnea/stridor</td>
<td>MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Cough/hemoptysis</td>
<td>MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td>Cervical nodes (rare with glottic CA)</td>
<td>MRI</td>
<td>Surgery and radiation Chemoradiotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Salivary Gland</strong></td>
<td>Painless mass (occ. pain is possible) CN VII palsy Cervical lymphadenopathy Rapid growth Invasion of skin Constitutional signs/symptoms</td>
<td>FNA MRI/CT/U/S</td>
<td>1° surgery ± neck dissection Post-operative radiotherapy Chemotherapy if unresectable</td>
</tr>
<tr>
<td>Parotid</td>
<td>MRI</td>
<td>Post-operative radiotherapy Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Cervical lymphadenopathy</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Rapid growth</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Invasion of skin</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Constitutional signs/symptoms</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td><strong>Thyroid</strong></td>
<td>Thyroid mass, cervical nodes Vocal cord paralysis Hyper/hypothyroidism Dysphagia</td>
<td>FNA U/S</td>
<td>1° surgery I131 for intermediate and high risk well differentiated thyroid cancer</td>
</tr>
<tr>
<td>Thyroid mass, cervical nodes</td>
<td>CT</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Vocal cord paralysis</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Hyper/hypothyroidism</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Dysphagia</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td><strong>Parathyroid</strong></td>
<td>Increased serum Ca2⁺</td>
<td>Sestamibi</td>
<td>Wide surgical excision Post-operative monitoring of serum Ca²⁺</td>
</tr>
<tr>
<td>Neck mass</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Bone disease, renal disease</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>MRI</td>
<td>Surgery and radiation Chemotherapy if unresectable</td>
<td></td>
</tr>
</tbody>
</table>
**Table 18. Bethesda Classification of Thyroid Cytology**

<table>
<thead>
<tr>
<th>Category</th>
<th>Risk of Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-diagnostic or unsatisfactory</td>
<td>Unknown</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
</tr>
<tr>
<td>Follicular lesion of undetermined significance/Atypia of undetermined significance</td>
<td>5-15%</td>
</tr>
<tr>
<td>Follicular/hürthle cell neoplasms</td>
<td>15-30%</td>
</tr>
<tr>
<td>Suspicious for malignancy</td>
<td>60-75%</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
</tr>
</tbody>
</table>

**Table 19. Thyroid Carcinoma**

<table>
<thead>
<tr>
<th>Papillary</th>
<th>Follicular</th>
<th>Medullary</th>
<th>Anaplastic</th>
<th>Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(70-75%)</td>
<td>10%</td>
<td>3 to 5%</td>
<td>&lt;5%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Route of Spread</td>
<td>Lymphatic</td>
<td>Hematogenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td>Orphan Annie nuclei</td>
<td>Psammoma bodies</td>
<td>Papillary architecture</td>
<td></td>
</tr>
<tr>
<td>Other Ps – Papillary cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fs – Follicular cancer</td>
<td>Far away mets</td>
<td>Female (3:1)</td>
<td>NOT FNA (cannot be diagnosed by FNA)</td>
<td>Favourable prognosis</td>
</tr>
<tr>
<td>Ms – Medullary cancer</td>
<td>Multiple endocrine neoplasia (MEN Ila or llb)</td>
<td>Amyloid</td>
<td>May secrete calcitonin, prostaglandins, ACTH, serotonin, kallikrein, or bradykinin</td>
<td>Giant cells</td>
</tr>
<tr>
<td>Prognosis</td>
<td>98% at 10 yr</td>
<td>92% at 10 yr</td>
<td>50% at 10 yr</td>
<td>20-35% at 1 yr</td>
</tr>
<tr>
<td>Treatment</td>
<td>Small tumours: Near total thyroidectomy or lobectomy Diffuse/bilateral: Total thyroidectomy ≥ post-operative 131 I scan to guide treatments</td>
<td>Small tumours: Total thyroidectomy</td>
<td>Total thyroidectomy</td>
<td>Radiation and chemotherapy Small tumours: Total thyroidectomy ± external beam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* B symptoms = fever, night sweats, chills, weight loss >10% in 6 mo  ** CHOP = cyclophosphamide, adriamycin, vincristine, prednisone

**Approach to Thyroid Nodule**

- all patients with thyroid nodules require evaluation of serum TSH and ultrasound
- any nodule >5 mm with suspicious sonographic features (particularly microcalcifications) should undergo FNA
- any nodule >1 cm should undergo FNA
- when performing repeat FNA on initially non-diagnostic nodules, U/S-guided FNA should be employed
- nuclear scanning has minimal value in the investigation of the thyroid nodule

**Table 20. Management of the Thyroid Nodule**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radioiodine therapy</td>
<td>For the treatment of hyperthyroidism or as adjuvant treatment after surgery in the treatment of papillary or follicular carcinoma</td>
</tr>
<tr>
<td>Chemotherapy and/or radiotherapy</td>
<td>Anaplastic CA or thyroid lymphoma</td>
</tr>
<tr>
<td>Surgical excision</td>
<td>Mass that is “suspicious” on FNA Malignancy other than anaplastic CA or thyroid lymphoma Mass that on FNA is benign but increasing in size on serial imaging and/or &gt;3-4 cm in size Hyperthyroidism not amenable to medical therapy</td>
</tr>
</tbody>
</table>

*US findings: cystic: risk of malignancy <1%; solid: risk of malignancy ~10%; solid with cystic components: risk of malignancy same as if solid
Acute Otitis Media

Definition
- all of: presence of middle ear effusion (MEE); presence of middle ear inflammation (MEI); acute onset of symptoms of MEE and MEI

Epidemiology
- most frequent diagnosis in sick children visiting clinicians’ offices and most common reason for antibiotic administration
- peak incidence between 6-15 mo; ~85% of children have >1 episode by 3 yr old
- seasonal variability: peaks in winter

Etiology
- primary defect causing AOM: Eustachian tube dysfunction/obstruction → stasis/colonization by pathogens
- bacterial: S. pneumoniae, non-typable H. influenzae, M. catarrhalis, Group A Streptococcus, S. aureus
- viral: RSV, influenza, parainfluenza, adenovirus
- commonly due to bacterial/viral co-infection

Predisposing Factors
- Eustachian tube dysfunction/obstruction
  - swelling of tubal mucosa
  - upper respiratory tract infection (URTI)
  - allergic rhinitis
  - chronic rhinosinusitis
- obstruction/infiltration of Eustachian tube ostium
  - tumour: nasopharyngeal carcinoma (adults)
  - adenoid hypertrophy (not due to obstruction but by maintaining a source of infection)
  - barotrauma (sudden changes in air pressure)
- inadequate tensor palati function: cleft palate (even after repair)
- abnormal Eustachian tube
  - Down syndrome (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
- disruption of action of
  - cilia of Eustachian tube: Kartagener’s syndrome
  - mucus secreting cells
  - capillary network that provides humoral factors, PMNs, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, cystic fibrosis

Risk Factors
- non-modifiable: young age, family history of OM, prematurity, orofacial abnormalities, immunodeficiencies, Down syndrome, race, and ethnicity
- modifiable: lack of breastfeeding, day care attendance, household crowding, exposure to cigarette smoke and air pollution, pacifier use

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers
  - ear-tugging (this alone is not a good indicator of pathology)
  - hearing loss, balance disturbances (rare)
  - irritable, poor sleeping
  - vomiting and diarrhea
  - anorexia
- otoscopy of TM
  - hyperemia
  - bulging, pus may be seen behind TM
  - loss of landmarks: handle and long process of malleus not visible

Clinical Assessment of AOM in Pediatrics
JAMA 2010;304:2161-2169
In assessment of AOM in pediatrics, ear pain is the most useful symptom with a likelihood ratio (LR) between 3.0-7.3. Useful otoscopic signs include erythematous (LR 8.4, 95% CI 7-11), cloudy (LR 34, 95% CI 28-42), bulging (LR 51, 95% CI 36-73), and immobile tympanic membrane (LR 31, 95% CI 26-37) on pneumatic otoscopy.
Diagnosis

- history
  - acute onset of otalgia or ear tugging in a preverbal child, otorrhea, decreased hearing
  - unexplained irritability, fever, upper respiratory symptoms, poor sleeping, anorexia, N/V, and diarrhea
- physical
  - febrile
  - MEE on otoscopy: immobile tympanic membrane, acute otorrhea, loss of bony landmarks, opacification of TM, air-fluid level behind TM
  - MEI on otoscopy: bulging TM with marked discoulouration (hemorrhagic, red, grey, or yellow)

Management

- observation for 48-72 h without antimicrobials may be appropriate since >80% of AOM in children resolve spontaneously
- criteria for watchful waiting approach
  - child is >6 mo old
  - child does not have immunodeficiency, chronic cardiac or pulmonary disease, anatomical abnormalities of the head or neck, a history of complicated otitis media (suppurative complications of chronic perforation) or Down syndrome
  - the illness is not severe – otalgia appears to be mild and fever is <39°C in the absence of antipyretics
  - parents are capable of recognizing signs of worsening illness and can readily access medical care if the child does not improve
  - antimicrobials are indicated if child does not meet the criteria for watchful waiting or does not improve/worsens during observation
- maintain hydration
- symptomatic relief: acetaminophen, ibuprofen
- referral to otolaryngology for myringotomy and tympanostomy tubes may be warranted for recurrent infections

Treatment

- antimicrobial agents for AOM
  - 1st line treatment (no penicillin allergy)
    - amoxicillin: 75 mg/kg/d to 90 mg/kg/d divided 3x/d
  - 2nd line treatment
    - cefprozil: 30 mg/kg/d divided 2x/d
    - cefuroxime axetil: 30 mg/kg/d divided 2x/d
    - ceftriaxone: 50 mg/kg intramuscularly (or intravenously) x 1 dose
    - azithromycin: 10 mg/kg OD x 1 dose, then 5 mg/kg OD x 4 doses
    - clarithromycin: 15 mg/kg/d divided 2x/d
  - if initial therapy fails (i.e. no symptomatic improvement after 2-3 d)
    - amoxicillin-clavulanate: 90 mg/kg/d amoxicillin, 6.4 mg/kg/d clavulanate divided 2x/d for 10 d
  - if AOM-related symptoms do not resolve with amoxicillin/clavulanate, a course of ceftriaxone 50 mg/kg/d intramuscularly (or intravenously) 1/d x 3 doses could be considered

Complications

- extracranial
  - hearing loss and speech delay (secondary to persistent MEE), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labrynthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction, persistent effusion (often leading to hearing loss)
- intracranial
  - meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis, facial nerve paralysis
- other
  - mastoiditis, labyrinthitis, sigmoid sinus thrombophlebitis

Otitis Media with Effusion

Definition

- presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology

- most common cause of pediatric hearing loss
- not exclusively a pediatric disease
- follows AOM frequently in children
- middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10%
Risk Factors
• same as AOM

Clinical Features
• conductive hearing loss ± tinnitus
  ▫ confirm with audiogram and tympanogram (flat) (see Figure 16B, OT10 and Figure 17B, OT11)
• fullness – blocked ear
• ± pain, low grade fever
• otoscopy of tympanic membrane
  ▫ discolouration – amber or dull grey with “glue” ear
  ▫ meniscus fluid level behind TM
  ▫ air bubbles
  ▫ retraction pockets/TM atelectasis
  ▫ most reliable finding with pneumotoscopy is immobility

Treatment
• expectant: 90% resolve by 3 mo
• document hearing loss with audiogram
• no clinical evidence that antihistamines, decongestants, or antibiotics clear disease faster
• surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes after first set falls out)
• ventilation tubes to equalize pressure and drain ear

Complications of Otitis Media with Effusion
• hearing loss, speech delay, learning problems in young children
• chronic mastoiditis
• ossicular erosion
• cholesteatoma especially when retraction pockets involve pars flaccida
• retraction of tympanic membrane, atelectasis, ossicular fixation

Adenoid Hypertrophy

• size peaks at age 5 and resolves by age 12
• increase in size with repeated URTI and allergies

Clinical Features
• nasal obstruction
  ▫ adenoid facies (open mouth, high arched palate, narrow midface, malocclusion)
  ▫ history of hypernasal voice and snoring
  ▫ long-term mouth breather; minimal air escape through nose
• choanal obstruction
  ▫ chronic rhinosinusitis/rhinitis
  ▫ obstructive sleep apnea
• chronic inflammation
  ▫ nasal discharge, post-nasal drip, and cough
  ▫ cervical lymphadenopathy

Diagnosis
• enlarged adenoids on nasopharyngeal exam (usually with flexible nasopharyngoscope)
• enlarged adenoid shadow on lateral soft tissue x-ray

Complications
• Eustachian tube obstruction leading to serous otitis media
• interference with nasal breathing, necessitating mouth-breathing
• malocclusion
• sleep apnea/respiratory disturbance
• orofacial developmental abnormalities

Adenoidectomy

Indications for Adenoidectomy
• chronic upper airway obstruction with sleep disturbance/apnea ± cor pulmonale
• chronic nasopharyngitis resistant to medical treatment
• chronic serous otitis media and chronic suppurrative otitis media (with 2nd set of tubes)
• recurrent acute otitis media resistant to antibiotics
• suspicion of nasopharyngeal malignancy
• persistent rhinorrhea secondary to nasal obstruction
Contraindications
• uncontrollable coagulopathy
• recent pharyngeal infection
• conditions that predispose to velopharyngeal insufficiency (cleft palate, impaired palatal function, or enlarged pharynx)

Complications
• bleeding, infection
• velopharyngeal insufficiency (hypernasal voice or nasal regurgitation)
• scarring of Eustachian tube orifice

Sleep-Disordered Breathing in Children

Definition
• spectrum of sleep-related breathing abnormalities ranging from snoring to OSA

Epidemiology
• peak incidence between 2-8 yr when tonsils and adenoids are the largest relative to the pharyngeal airway

Etiology
• due to a combination of anatomic and neuromuscular factors
  ▪ adenotonsillar hypertrophy
  ▪ craniofacial abnormalities
  ▪ neuromuscular hypotonia (i.e. cerebral palsy, Down syndrome)
  ▪ obesity

Clinical Features
• heavy snoring, mouth breathing, pauses or apnea, enuresis, excessive daytime sleepiness, behavioural/learning problems, diagnosis of ADHD, morning headache, failure to thrive

Investigations
• flexible nasopharyngoscopy for assessment of nasopharynx and adenoids
• polysomnography (apnea-hypopnea index >1/h considered abnormal)

Treatment
• surgical: bilateral tonsillectomy and adenoidectomy
• nonsurgical: CPAP, BiPAP, sleep hygiene

Acute Tonsillitis
• see Pediatrics, P58

Peritonsillar Abscess (Quinsy)

Definition
• cellulitis of space behind tonsillar capsule extending onto soft palate leading to abscess

Etiology
• bacterial: Group A strep (GAS) (50% of cases), S. pyogenes, S. aureus, H. influenzae, and anaerobes

Epidemiology
• can develop from acute tonsillitis with infection spreading into plane of tonsillar bed
• unilateral
• most common in 15-30 yr age group

Clinical Features
• fever and dehydration
• sore throat, dysphagia, and odynophagia
• extensive peritonsillar swelling but tonsil may appear normal
• edema of soft palate
• uvular deviation
• trismus (due to irritation and reflex spasm of the medial pterygoid)
• dysphonia (edema → failure to elevate palate) 2º to CN X involvement
• unilateral referred otalgia
• cervical lymphadenitis

Quinsy Triad
• Trismus
• Uvular deviation
• Dysphonia ("hot potato voice")
Complications
- aspiration pneumonia 2º to spontaneous rupture of abscess
- airway obstruction
- lateral dissection into parapharyngeal and/or carotid space
- bacteremia
- retropharyngeal abscess

Treatment
- secure airway
- surgical drainage (incision or needle aspiration) with C&S
- warm saline irrigation
- IV penicillin G x 10 d if cultures positive for GAS
- add PO/IV metronidazole or clindamycin x 10 d if culture positive for Bacteroides
- consider tonsillectomy after second episode

Other Sources of Parapharyngeal Space Infections
- pharyngitis
- acute suppurative parotitis (see Salivary Glands, OT30)
- AOM
- mastoiditis (Bezold's abscess)
- odontogenic infection

Tonsillectomy

Absolute Indications
- most common indication: sleep-disordered breathing
- 2nd most common indication: recurrent throat infections
- tonsillar hypertrophy causing upper airway obstruction, obstructive sleep apnea, severe dysphagia, or cardiopulmonary complications such as cor pulmonale
- suspicion of malignancy (e.g. lymphoma, squamous cell carcinoma)
- orofacial/dental deformity
- hemorrhagic tonsillitis

Relative Indications (To Reduce Disease Burden)
- recurrent throat infection with a frequency of at least 7 episodes in the past year, at least 5 episodes per year for 2 yr, or at least 3 episodes per year for 3 yr, with documentation in the medical record for each episode of sore throat and 1 or more of the following: temperature >38.3°C, cervical adenopathy, tonsillar exudate, or positive test for Group A β-hemolytic streptococcus (Paradise Criteria)
- chronic tonsillitis with halitosis (bad breath) or sore throat ± tonsilloliths (clusters of calcified material that form in the crevices of the tonsils)
- complications of tonsillitis: quinsy/peritonsillar abscess, parapharyngeal abscess, retropharyngeal abscess
- failure to thrive

Relative Contraindications
- velopharyngeal insufficiency: overt or submucous/covert cleft of palate, impaired palatal function due to neurological or neuro-muscular abnormalities
- hematologic: coagulopathy, anemia
- infectious: active local infection without urgent obstructive symptoms

Complications
- hemorrhage: early (within 24 h); delayed (within 7-10 d)
- odynophagia and/or otalgia; dehydration 2º to odynophagia
- infection
- atlantoaxial subluxation (Grisel's syndrome) - rare

Airway Problems in Children

Differential Diagnosis by Age Group

Neonates (Obligate Nose Breeders)
- extralaryngeal
  - choanal atresia (e.g. CHARGE syndrome)
  - nasopharyngeal dermoid, glioma, encephalocele
  - glossoptosis: Pierre-Robin sequence, Down syndrome, lymphatic malformation, hemangioma
- laryngeal
  - laryngomalacia: most common cause of stridor in children
  - laryngocele
- vocal cord palsy (due to trauma or Arnold-Chiari malformation)
- glottic web
- subglottic stenosis
- laryngeal cleft
- tracheal
  - tracheoesophageal fistula
  - tracheomalacia
  - vascular rings

**2-3 Months**
- congenital
  - laryngomalacia
  - vascular: subglottic hemangioma (more common), innominate artery compression, double aortic arch
  - laryngeal papilloma
- acquired
  - subglottic stenosis: post-intubation
  - tracheal granulation: post-intubation
  - tracheomalacia: post-tracheotomy and TEF repair

**Infants – Sudden Onset**
- foreign body aspiration
- croup
- bacterial tracheitis
- caustic ingestion
- epiglottitis

**Children and Adults**
- infection
  - Ludwig's angina
  - peritonsillar/parapharyngeal abscess
  - retropharyngeal abscess
- neoplastic
  - squamous cell carcinoma (SCC) (adults): larynx, hypopharynx
  - retropharyngeal: lymphoma, neuroblastoma
  - nasopharyngeal: carcinoma, rhabdomyosarcoma
- allergic
  - angioneurotic edema
  - polyps (suspect cystic fibrosis in children)
- trauma
  - laryngeal fracture, facial fracture
  - burns and lacerations
  - post-intubation
  - caustic ingestion
- congenital
  - lingual thyroid/tonsil

---

**Signs of Airway Obstruction**

**Stridor**
- note quality, timing (inspiratory or expiratory)
- body position important
  - lying prone: subglottic hemangioma, double aortic arch
  - lying supine: laryngomalacia, glossoptosis
- site of stenosis
  - vocal cords or above: inspiratory stridor
  - subglottis and extrathoracic trachea: biphasic stridor
  - distal tracheobronchial tree: expiratory stridor

**Respiratory Distress**
- nasal flaring
- supraclavicular and intercostal indrawing
- sternal retractions
- use of accessory muscles of respiration
- tachypnea
- cyanosis
- altered LOC
Feeding Difficulty and Aspiration
- supraglottic lesion
- laryngomalacia
- vocal cord paralysis
- laryngeal cleft → aspiration pneumonia
- TEF

**Acute Laryngotracheobronchitis (Croup)**
- inflammation of tissues in subglottic space ± tracheobronchial tree
- swelling of mucosal lining and associated with thick, viscous, mucopurulent exudate which compromises upper airway (subglottic space narrowest portion of upper airway)
- normal function of ciliated mucous membrane impaired

**Etiology**
- viral: parainfluenzae I (most common), II, III, influenza A and B, RSV

**Clinical Features**
- age: 4 mo-5 yr
- preceded by URTI symptoms
- generally occurs at night
- biphasic stridor and croupy cough (loud, sea-lion bark)
- appear less toxic than epiglottitis
- supraglottic area normal
- rule out foreign body and subglottic stenosis
- "steeple-sign" on AP x-ray of neck
- if recurrent croup, think subglottic stenosis

**Treatment**
- racemic epinephrine via MDI q1-2h, prn (only if in respiratory distress)
- systemic corticosteroids (e.g. dexamethasone, prednisone)
- adequate hydration
- close observation for 3-4 h
- intubation if severe
- hospitalize if poor response to steroids after 4 h and persistent stridor at rest
- consider alternate diagnosis if poor response to therapy (e.g. bacterial tracheitis)
- if recurrent episodes of croup-like symptoms, consider bronchoscopy several weeks after acute episode settles to rule out underlying subglottic stenosis

**Acute Epiglottitis**
- acute inflammation causing swelling of supraglottic structures of the larynx without involvement of vocal cords

**Etiology**
- *H. influenzae* type b
- relatively uncommon condition due to Hib vaccine

**Clinical Features**
- any age, most commonly 1-4 yr
- rapid onset
- toxic-looking, fever, anorexia, restlessness
- cyanotic/pale, inspiratory stridor, slow breathing, lungs clear with decreased air entry
- prefers sitting up ("tripod" posture), open mouth, drooling, tongue protruding, sore throat, dysphagia

**Investigations and Management**
- investigations and physical exam may lead to complete obstruction, thus preparations for intubation or tracheotomy must be made prior to any manipulation
- stat ENT/anesthesia consult(s)
- WBC (elevated), blood and pharyngeal cultures after intubation
- lateral neck radiograph (only done if patient stable)

**Treatment**
- secure airway
- IV access with hydration
- antibiotics: IV cefuroxime, cefotaxime, or ceftriaxone
- moist air
- extubate when leak around tube occurs and afebrile
- watch for meningitis
Subglottic Stenosis

Congenital
• diameter of subglottis <4 mm in neonate (due to thickening of soft tissue of subglottic space or maldevelopment of cricoid cartilage)

Acquired
• following prolonged, repeated, or traumatic intubation
  ▪ most commonly due to endotracheal intubation; nasal intubation is less traumatic and preferred in long-term intubation as it puts less pressure on the subglottis (tube sits at different orientation) and there is less movement
  ▪ subglottic stenosis is related to duration of intubation and pressure of the endotracheal tube cuff
• can also be due to foreign body, infection (e.g. TB, diphtheria, syphilis), or chemical irritation

Clinical Features
• biphasic stridor
• respiratory distress
• recurrent/prolonged croup

Diagnosis
• rigid laryngoscopy and bronchoscopy

Treatment
• if soft stenosis: divide tissue with knife or laser, dilate with balloon ± steroids
• if firm stenosis: laryngotracheoplasty

Laryngomalacia
• short aryepiglottic folds, omega-shaped epiglottis, pendulous mucosa
• caused by indrawing of supraglottis on inspiration leading to laryngopharyngeal reflux of acid

Clinical Features
• high-pitched inspiratory stridor at 1-2 wk
• constant or intermittent and more pronounced supine and following URTI
• usually mild but when severe can be associated with cyanosis or feeding difficulties, leading to failure to thrive

Treatment
• observation is usually sufficient as symptoms spontaneously subside by 12-18 mo in >90% of cases
• if severe, division of the aryepiglottic folds (supraglottoplasty) provides relief

Foreign Body

Ingested
• usually stuck at cricopharyngeus
• coins, toys, batteries (emergency)
• presents with drooling, dysphagia, stridor if very large

Aspirated
• usually stuck at right mainstem bronchus
• peanuts, carrot, apple core, popcorn, balloons
• presentation
  ▪ stridor if lodged in trachea
  ▪ unilateral “asthma” if bronchial, therefore often misdiagnosed as asthma
  ▪ if totally occludes airway: cough, lobar pneumonia, atelectasis, mediastinal shift, pneumothorax, death

Diagnosis and Treatment
• any patient with suspected foreign body should be kept NPO immediately
• inspiration-expiration chest x-ray (if patient is stable)
• bronchoscopy or esophagoscopy with removal
• rapid onset, not necessarily febrile or elevated WBC
**Deep Neck Space Infection**

- most commonly arise from an infection of the mandibular teeth, tonsils, parotid gland, deep cervical lymph nodes, middle ear, or the sinuses
- often a rapid onset and may progress to fatal complications

**Etiology**
- usually mixed aerobes and anaerobes that represent the flora of the oral cavity, upper respiratory tract, and certain parts of the ears and eyes

**Clinical Features**
- sore throat or pain and trismus
- dysphagia and odynophagia
- stridor and dyspnea
- late findings may include dysphonia and hoarseness
- swelling of the face and neck, erythema
- asymmetry of the oropharynx with purulent oral discharge
- lymphadenopathy

**Diagnosis**
- lateral cervical view plain radiograph
- CT
- MRI

**Treatment**
- secure the airway
- surgical drainage
- maximum doses of IV systemic antimicrobials regimens according to the site of infection

---

**Common Medications**

**Table 21. Antibiotics**

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>amoxicillin (Amoxil®, Amox®, Amox®)</td>
<td>Adult: 500 mg PO tid, Children: 75-90 mg/kg/d in 2 divided doses</td>
<td>Streptococcus, Pneumococcus, H. influenzae, Proteus coverage</td>
<td>May cause rash in patients with infectious mononucleosis</td>
</tr>
<tr>
<td>piperacillin with tazobactam (Zosyn®)</td>
<td>3 g PO q6h</td>
<td>Gram-positive and negative aerobes and anaerobes plus Pseudomonas coverage</td>
<td>May cause pseudomembranous colitis</td>
</tr>
<tr>
<td>ciprofloxacin (Cipro®, Ciloxan®)</td>
<td>500 mg PO bid</td>
<td>Pseudomonas, Streptococci, MRSA, and most Gram-negative; no anaerobic coverage</td>
<td>Do not give systemic quinolones to children</td>
</tr>
<tr>
<td>erythromycin (Erythrocin®, EryPed®, Staticin®, T-Stat®, Erybid®, Novorythro Encap®)</td>
<td>500 mg PO qid</td>
<td>Alternative to penicillin, Ototoxic</td>
<td></td>
</tr>
</tbody>
</table>

**Table 22. Otic Drops**

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Dose</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ciprofloxacin (Ciprodex®)</td>
<td>4 gtt in affected ear bid</td>
<td>For otitis externa and complications of otitis media</td>
<td></td>
</tr>
<tr>
<td>neomycin, polymyxin B sulfate, and hydrocortisone (Consporin Otic®)</td>
<td>5 gtt in affected ear tid</td>
<td>For otitis externa, Used for inflammatory conditions which are currently infected or at risk of bacterial infections</td>
<td>May cause hearing loss if placed in inner ear</td>
</tr>
<tr>
<td>hydrocortisone and acetic acid (NoSol HE®)</td>
<td>5-10 gtt in affected ear tid</td>
<td>For otitis media</td>
<td>Bactericidal by lowering pH</td>
</tr>
<tr>
<td>tobramycin and dexamethasone (TobraDex®)</td>
<td>5-10 gtt in affected ear bid</td>
<td>For chronic suppurative otitis media</td>
<td>Risk of vestibular or cochlear toxicity</td>
</tr>
</tbody>
</table>
Table 23. Nasal Sprays

<table>
<thead>
<tr>
<th>Generic Name (Brand Name)</th>
<th>Indications</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>flunisolide (Rhinalair&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Allergic rhinitis</td>
<td>Requires up to 4 wk of consistent use to have effect</td>
</tr>
<tr>
<td>budesonide (Rhinocort&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Chronic sinusitis</td>
<td>Long-term use</td>
</tr>
<tr>
<td>triamcinolone (Nasacort&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td>Dries nasal mucosa; may cause minor bleeding</td>
</tr>
<tr>
<td>beclomethasone (Beconase&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td>Patient should stop if epistaxis</td>
</tr>
<tr>
<td>mometasone furoate, monohydrate (Nasonex&lt;sup&gt;®&lt;/sup&gt;)</td>
<td></td>
<td>May sting</td>
</tr>
<tr>
<td>fluticasone furoate (Avamys&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Flonase&lt;sup&gt;®&lt;/sup&gt; and Nasonex&lt;sup&gt;®&lt;/sup&gt; not absorbed systemically</td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>levocabastine (Livostin&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Allergic rhinitis</td>
<td>Immediate effect</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If no effect by 3 d then discontinue Use during allergy season</td>
</tr>
</tbody>
</table>

| Decongestant             |             |       |
| xylometazoline (Otrivin<sup>®</sup>) | Acute sinusitis | Careful if patient has hypertension |
| oxymetazoline (Drisana<sup>®</sup>) | Rhinitis | Short-term use (<5 d) |
| phenylephrine (Neosynephrine<sup>®</sup>) | | If long-term use, can cause decongestant addiction (i.e. rhinitis medicamentosa) |

| Antibiotic/Decongestant  |             |       |
| frarnycetin, gramicidin, phenylephrine (Soframycin<sup>®</sup>) | Acute sinusitis | |

| Anticholinergic          |             |       |
| ipratropium bromide (Atrovent<sup>®</sup>) | Vasomotor rhinitis | Careful not to spray into eyes as can cause burning or precipitation of narrow angle glaucoma |

| Lubricants               |             |       |
| saline, NeilMed<sup>®</sup>, Rhinaris<sup>®</sup> | Dry nasal mucosa | Use prn |
| Secaris<sup>®</sup>, Polysporin<sup>®</sup>, Vaseline<sup>®</sup> | | Rhinaris<sup>®</sup> and Secaris<sup>®</sup> may cause stinging |

Source: Dr. MM Carr

References

Hilton M, Pinder D. The Epley (canalith repositioning) maneuver for benign paroxysmal positional vertigo. Careful if patient has hypertension.


Source: Dr. MM Carr
### Acronyms
- Hypercalcemia/Hypocalcemia/Rickets
- Hyperthyroidism and Hypothyroidism
- Sexual Development

### Pediatric Quick Reference Values

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<td>Constipation</td>
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Acronyms

AAP American Academy of Pediatrics
ABD arterial blood gas
ACE angiotensin converting enzyme
ALL acute lymphoblastic leukemia
ALPS autoimmune lymphoproliferative syndrome
ALT E acute liver-threatening event
AML acute myelogenous leukemia
ANA antinuclear antibody
AOI acute otitis media
ARB angiotensin receptor blocker
ARBD alcohol-related birth defects
ARND alcohol-related neurodevelopmental disorder
ASD atrial septal defect
ASOT antistreptolysin-O titer
ATN acute tubular necrosis
AVM arteriovenous malformation
CAH congenital adrenal hyperplasia
CAS Children’s Aid Society
CF cystic fibrosis
CHD congenital heart defect
CML chronic myelogenous leukemia
CP cerebral palsy
CPS Canadian Pediatric Society
DSAV 1-desamino-8-D-arginine vasopressin
DC diabetes insipidus
DCC disseminated intravascular coagulation
DKA diabetic ketoacidosis

Table 1. Average Vitals at Various Ages

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Pulse (bpm)</th>
<th>Respiratory Rate (br/min)</th>
<th>sBP (mmHg)</th>
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<tr>
<td>&lt;1</td>
<td>110-180</td>
<td>30-40</td>
<td>70-90</td>
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<tr>
<td>1-2</td>
<td>100-150</td>
<td>25-35</td>
<td>80-95</td>
</tr>
<tr>
<td>2-5</td>
<td>95-140</td>
<td>25-35</td>
<td>80-100</td>
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<tr>
<td>5-12</td>
<td>80-120</td>
<td>20-25</td>
<td>90-110</td>
</tr>
<tr>
<td>&gt;12</td>
<td>60-100</td>
<td>15-20</td>
<td>110-120</td>
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Primary Care

Visit Overview

- schedule
  - newborn (within 1 wk post-discharge), 1, 2, 4, 6, 9, 12, 15, 18, 24 mo
  - annually between age 2-5; every 1-2 years between age 6-18
- content
  - history and physical exam including growth, development, and nutrition
  - routine immunizations
  - counselling and anticipatory guidance

Routine Immunization

Table 2. Publicly Funded Immunization Schedule for Ontario, August 2011

<table>
<thead>
<tr>
<th>Age</th>
<th>DTaP IPV-Hib</th>
<th>dTaP IPV</th>
<th>Pneu- C-13</th>
<th>Rot-1</th>
<th>Men- C-C</th>
<th>MMR</th>
<th>Var</th>
<th>MMRV</th>
<th>Men-C-ACYW</th>
<th>HepB</th>
<th>HPV-4</th>
<th>Tdap</th>
<th>Inf</th>
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<tr>
<td>2 mo</td>
<td>✓ IM</td>
<td>✓ IM</td>
<td>✓ PO</td>
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<td>✓ SC</td>
<td>✓ IM</td>
<td>✓ SC</td>
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<td>4 mo</td>
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<td>✓ PO</td>
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<td>✓ IM/SC</td>
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<td>✓ SC</td>
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<td>✓ SC</td>
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<tr>
<td>6 mo</td>
<td>✓ IM</td>
<td>✓ IM</td>
<td>✓ PO</td>
<td>✓ IM</td>
<td>✓ IM/SC</td>
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<td>✓ SC</td>
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<td>✓ SC</td>
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<td>12 mo</td>
<td>✓ IM</td>
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<td>✓ SC</td>
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<td>15 mo</td>
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<td>✓ SC</td>
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<td>Every autumn</td>
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<td>✓ PO</td>
<td>✓ IM</td>
<td>✓ IM/SC</td>
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<td>✓ IM</td>
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IM = intramuscular; PO = per oral; SC = subcutaneous

Available at: http://www.phac-aspc.gc.ca/publicat/cig-gci/

According to the CDC, the weight of currently available scientific evidence does not support the hypothesis that MMR vaccine causes either autism or IBD. The landmark paper linking autism to the MMR vaccine (Lancet 1998;351:637-641) was retracted due to false claims in the article (Lancet 2010;375:648).
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<th>Contraindication</th>
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<td>Prolonged crying</td>
<td>Evolving unstable neurologic disease</td>
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<tr>
<td></td>
<td>Hypotonic</td>
<td>Hyporesponsive/hypotonic following previous vaccine</td>
</tr>
<tr>
<td></td>
<td>unresponsive state (rare)</td>
<td>Anaphylactic reaction to neomycin or streptomycin</td>
</tr>
<tr>
<td>Rot-1</td>
<td>Cough</td>
<td>History of intussusception</td>
</tr>
<tr>
<td></td>
<td>Diarrhea, vomiting</td>
<td>Immunocompromised</td>
</tr>
<tr>
<td></td>
<td>Abdominal disorder (e.g. Meckel’s diverticulum)</td>
<td>Received blood products (e.g. immunoglobulin) within 42 d</td>
</tr>
<tr>
<td>MMR</td>
<td>Measle-like rash (7-14 d)</td>
<td>Pregnancy</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy, arthralgia, arthritis</td>
<td>Immunocompromised</td>
</tr>
<tr>
<td></td>
<td>Parotitis (rare)</td>
<td>Abdominal disorder (e.g. Meckel’s diverticulum)</td>
</tr>
<tr>
<td></td>
<td>Especially painful injection</td>
<td>Anaphylactic reaction to gelatin</td>
</tr>
<tr>
<td>Var</td>
<td>Mild varicella-like papules or vesicles</td>
<td>Pregnant or planning to get pregnant within 3 mo</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anaphylactic reaction to gelatin</td>
</tr>
<tr>
<td>HepB</td>
<td></td>
<td>Anaphylactic reaction to Baker’s yeast</td>
</tr>
<tr>
<td>MMRV</td>
<td>Same as MMR and Var vaccines</td>
<td>Same as MMR and Var vaccines</td>
</tr>
<tr>
<td>dTAP</td>
<td></td>
<td>1st trimester pregnancy</td>
</tr>
<tr>
<td>Inf</td>
<td>Malaise, myalgia</td>
<td>&lt;6 months of age</td>
</tr>
<tr>
<td></td>
<td>Febrile seizure when given with Pneu-C 13</td>
<td>Egg-allergic individuals – Live attenuated influenza vaccine is not recommended for those with an egg allergy. In these individuals, trivalent or quadrivalent vaccine can be given in environment where anaphylaxis may be anticipated.</td>
</tr>
<tr>
<td>HPV-4</td>
<td>Pruritis</td>
<td>Anaphylactic reaction to MenB vaccine or its components in the past</td>
</tr>
<tr>
<td>MenB*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Publicly Funded Immunization Schedule for Ontario, August 2011 (continued)**

- **Injection site**
  - Infants (<12 mo): anterolateral thigh
  - Children: deltoid, subcutaneous tissue of the upper triceps area of the arm (IM injections should be given at 90° angle; SC injections should be given at 45° angle)

- **Timing of injection**
  - Varicella and MMR vaccines given at either the same visit or separated by >4 wk (MMRV at 4–6 yr)
  - Hepatitis B vaccine given in 3 doses of 0.5 mL (0, 1, 6 mo) either at school in grade 7 (2 adult doses of 1 mL one month apart for teens) (Ontario) or at birth if at increased risk (i.e. endemic country, mother or household contact HBsAg positive)
  - HPV-4 vaccine given in 3 doses (0, 2, 6 mo) to grade 8 females in Ontario schools

**Adverse Reactions**

- Local: injection site reactions
- Systemic: fever, rash, irritability

**Contraindications**

- Moderate/severe illness: contraindication
- Allergy to vaccine component
- No need to delay vaccination for mild URI

- Any Vaccine
  - Local: injection site reactions
  - Systemic: fever, rash, irritability
  - Allergic: urticaria, rhinitis, anaphylaxis

**Vaccination in Cases of Asplenia or Hyposplenia**

- Should receive all routine immunizations, including the yearly influenza vaccine
- No vaccines are contraindicated
- Susceptible to infection by encapsulated bacteria (S. pneumoniae, H. influenzae, N. meningitidis), so must add:
  - Meningococcal C-Conjugate at age >2 yr + Quadrivalent Men-P-ACYW at least 2 wk later
  - Booster of Men-P-ACYW q2-yr
  - Pneumococcal polysaccharide vaccine (Pneu-P-23) at age >2 yr
  - Single booster of Pneu-P-23 at age >3 yr
  - Consider single booster HB at age >5 yr

**Safety and Efficacy of an Attenuated Vaccine Against Severe Rotavirus Gastroenteritis**

- **Study:** Randomized, double-blind, phase 3 trial.
- **Patients:** 61,225 healthy infants from Latin America and Finland.
- **Intervention:** Two oral doses of HRV vaccine vs. placebo at 2 and 4 mo of age.
- **Results:** The vaccine is 85% efficacious against severe rotavirus gastroenteritis and hospitalizations associated with gastroenteritis and 100% efficacious against more severe gastroenteritis.

**Growth and Development**

- **Growth**
  - Growth is not linear
  - Most rapid growth during first 2 yr and at puberty
  - Tissues grow at different times
    - First 2 yr = CNS; mid-childhood = lymphoid tissue; puberty = gonads
  - Measurement of growth
    - Premature infants (<37 wk) use corrected GA until age 2
    - Body proportion = upper/lower segment ratio (use symphysis pubis as midpoint)
    - Newborn = 1.7, adult male = 0.9, adult female = 1.0

**Scoliosis Screening**

- Despite mass school screening implemented in parts of the USA and Canada in the 1970s-90s, the Canadian (1994) and American (2004) Task Forces on Preventive Health Care do NOT currently recommend routine screening using the Forward Bend Test (FBT). Cohort studies indicate that the Forward Bend Test has poor sensitivity for identifying pathological curves. Furthermore, there is no evidence to suggest that screening and increased bracing lead to better outcomes
Average Growth Parameters

Table 3. Parameter of Average Growth at Birth

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Growth</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight</td>
<td>3.25 kg (7 lbs)</td>
<td>Gain 20-30 g/d (term neonate)</td>
<td>Weight loss (up to 10% of birth weight) in first 7 d of life is normal. Neonate should regain birth weight by ~10-14 d of age.</td>
</tr>
<tr>
<td></td>
<td>2 x birth wt by 4-5 mo</td>
<td>3 x birth wt by 1 yr</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 x birth wt by 2 yr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length/Height</td>
<td>50 cm (20 in)</td>
<td>25 cm in 1st yr</td>
<td>Measure supine length until 2 yr of age, then measure standing height</td>
</tr>
<tr>
<td></td>
<td>12 cm in 2nd yr</td>
<td>8 cm in 3rd yr then</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4-7 cm/yr until puberty</td>
<td>1/2 adult height at 2 yr</td>
<td></td>
</tr>
<tr>
<td>Head Circumference</td>
<td>35 cm (14 in)</td>
<td>2 cm/mo for 1st 3 mo</td>
<td>Measure around occipital, parietal, and frontal prominences to obtain the greatest circumference</td>
</tr>
<tr>
<td></td>
<td>1 cm/mo at 3-6 mo</td>
<td>0.5 cm/mo at 6-12 mo</td>
<td></td>
</tr>
</tbody>
</table>

Reflexes

Table 4. Reflexes

<table>
<thead>
<tr>
<th>Reflex</th>
<th>Maneuver to Elicit Reflex</th>
<th>Appropriate Reflex Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moro</td>
<td>Infant placed semi-upright, head supported by examiner’s hand, sudden withdrawal of supported head with immediate return of support</td>
<td>Abduction and extension of the arms, opening of the hands, followed by flexion and adduction of arms</td>
</tr>
<tr>
<td>Galant</td>
<td>Infant held in ventral suspension and one side of back is stroked along paravertebral line</td>
<td>Pelvis will move in the direction of stimulated side</td>
</tr>
<tr>
<td>Grasp</td>
<td>Placement of examiner’s finger in infant’s palm</td>
<td>Flexion of infant’s fingers</td>
</tr>
<tr>
<td>ATNR</td>
<td>Turn infant’s head to one side</td>
<td>“Fencing” posture (extension of ipsilateral leg and arm and flexion of contralateral arm)</td>
</tr>
<tr>
<td>Placing</td>
<td>Dorsal surface of infant’s foot placed touching edge of table</td>
<td>Flexion followed by extension of ipsilateral limb up onto table (resembles primitive walking)</td>
</tr>
<tr>
<td>Rooting</td>
<td>Tactile stimulus near mouth</td>
<td>Infant pursues stimulus with face</td>
</tr>
<tr>
<td>Parachute</td>
<td>Tilt infant to side while in sitting position</td>
<td>Ipsilateral arm extension, present by 6-8 mo</td>
</tr>
</tbody>
</table>

ATNR = asymmetric tonic neck reflex

Abnormal Reflex Response

- Absence may suggest CNS abnormality
- Persistence after 4-6 mo may indicate abnormality (e.g. cerebral palsy)
- Asymmetry suggests focal motor lesions (e.g. brachial plexus injury)
- Upgoing plantar reflex (Babinski’s sign) normal in infants up to age 2 yr

Developmental Milestones

Table 5. Developmental Milestones

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>Tums head side to side when supine</td>
<td>Hands fist, thumb in fist</td>
<td>Cries, startles to loud noises</td>
<td>Calms when comforted</td>
</tr>
<tr>
<td>2 mo</td>
<td>Briefly raises head when prone, holds head erect when upright</td>
<td>Pulls at clothes</td>
<td>Variety of sounds (e.g. coos, gurgles)</td>
<td>Smiles responsively, recognizes and calms down to familiar voice, follows movement with eyes</td>
</tr>
<tr>
<td>4 mo</td>
<td>Lifts head and chest when prone, holds head steady when supported sitting, rolls prone to supine</td>
<td>Briefly holds object when placed in hand, reaches for midline objects</td>
<td>Turns head towards sounds</td>
<td>Laughs responsively, follows moving toy or person with eyes, responds to people with excitement (e.g. leg movement)</td>
</tr>
<tr>
<td>6 mo</td>
<td>Tripod sit, pivots in prone position</td>
<td>Ulnar or raking grasp, transfers objects from hand to hand, brings objects to mouth</td>
<td>Babbles</td>
<td>Stranger anxiety, beginning of object permanence</td>
</tr>
<tr>
<td>9 mo</td>
<td>Sits well without support, crawls, pulls to stand, stands with support</td>
<td>Early pincer grasp with straight wrist</td>
<td>“Mama, dada” – appropriate, imitates 1 word, responds to “no” regardless of tone</td>
<td>Plays games (e.g. peek-a-boo), reaches to be picked up</td>
</tr>
<tr>
<td>12 mo</td>
<td>Gets into sitting position without help, stands without support, walks while holding on</td>
<td>Neat pincer grasp, releases ball with throw</td>
<td>2 words, follows 1-step command, uses facial expression, sounds, actions to make needs known</td>
<td>Responds to own name, separation anxiety begins</td>
</tr>
</tbody>
</table>

*Use corrected GA until 2 yr

Developmental Red Flags

- Gross motor: not walking at 18 mo
- Fine motor: handedness at <10 mo
- Speech: <3 words at 18 mo
- Social: not smiling at 3 mo; not pointing at 15-18 mo
- See the Nipissing District Developmental Screen for a checklist of important 18 mo milestones: www.ndds.ca
Table 5. Developmental Milestones (continued)

<table>
<thead>
<tr>
<th>Age*</th>
<th>Gross Motor</th>
<th>Fine Motor</th>
<th>Speech and Language</th>
<th>Adaptive and Social Skills</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 mo</td>
<td>Walks without support, crawls up stairs/steps</td>
<td>Picks up and eats finger foods, scribbles, stacks 2 blocks</td>
<td>4-5 words, points to needs/wants</td>
<td>Looks to see how others react (e.g. after falling)</td>
</tr>
<tr>
<td>18 mo</td>
<td>Runs, walks forward pulling toys or carrying objects</td>
<td>Tower of 3 cubes, scribbling, eats with spoon</td>
<td>10 words, follows simple commands</td>
<td>Shows affection towards others, points to show interest in something</td>
</tr>
<tr>
<td>24 mo</td>
<td>Climbs up and down steps with 2 feet per step, runs, kicks ball</td>
<td>Tower of 6 cubes, undresses</td>
<td>2-3 word phrases, uses “I, me, you”, 50% intelligible, understands 2-step commands</td>
<td>Parallel play, helps to dress</td>
</tr>
<tr>
<td>3 yr</td>
<td>Rides tricycle, climbs up 1 foot per step, down 2 feet per step, stands on one foot briefly</td>
<td>Copies a circle, turns pages one at a time, puts on shoes, dress/undress fully except buttons</td>
<td>Combines 3 or more words into sentence, recognizes colours, prepositions, plurals, counts to 10, 75% intelligible</td>
<td>Knows sex and age, shares some of the time, plays make-believe games</td>
</tr>
<tr>
<td>4 yr</td>
<td>Hops on 1 foot, climbs down 1 foot per step</td>
<td>Copies a cross, uses scissors, buttons clothes</td>
<td>Speech 100% intelligible, uses past tense, understands 3-part directions</td>
<td>Cooperative play, fully toilet-trained by day, tries to comfort someone who is upset</td>
</tr>
<tr>
<td>5 yr</td>
<td>Skips, rides bicycle</td>
<td>Copies a triangle and square, prints name, ties shoelaces</td>
<td>Fluent speech, future tense, alphabet, retells sequence of a story</td>
<td>Cooperates with adult requests most of the time, separates easily from caregiver</td>
</tr>
</tbody>
</table>

*Use corrected GA until 2 yr

**Nutrition**

**Dietary Requirements**

<table>
<thead>
<tr>
<th>Weight</th>
<th>Needs</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 kg</td>
<td>100 kcal/kg/d</td>
</tr>
<tr>
<td>10-20 kg</td>
<td>1,000 cal + 50 kcal/kg/d for each kg &gt;10</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>1,500 cal + 20 kcal/kg/d for each kg &gt;20</td>
</tr>
</tbody>
</table>

**Dietary Recommendations**

- 0-6 mo: breast milk or formula
  - exclusive breast milk during first 6 mo recommended over formula unless contraindicated
  - breastfed infants require supplements: vitamin K (all babies get at birth, breastfed or not), vitamin D (400-800 IU/d), fluoride (after 6 mo if not sufficient in water), iron (6-12 mo, only if not receiving fortified cereals/meat/meat alternatives)
- >6 mo: solid food introduction – do not delay beyond 9 mo
  - 2-3 new foods per wk with a few days in between each food to allow time for adverse reaction identification
  - suggested order of introduction
    - meat, meat alternatives, and iron-enriched cereal (rice cereal is least allergenic)
    - pureed vegetables
    - fruit
- 9-12 mo: finger foods and switch to homogenized (3%) milk
  - feed child based on hunger/satiety cues; encourage self-feeding and introduce open cup
  - foods to avoid
    - honey until past 12 mo (risk of botulism)
    - added sugar, salt
    - excessive milk (i.e. no more than 16 oz/d after 1 yr)
    - juice (not nutritious, too much sugar)
    - anything that is a choking hazard (chunks, round foods like grapes)

**Breastfeeding**

- content of breast milk
  - colostrum (first few days): clear, rich in nutrients (i.e. high protein, low fat), immunoglobulin
  - mature milk: 70:30 whey:casein ratio, fat from dietary butterfat, carbohydrate from lactose
- advantages
  - easily digested, low renal solute load
  - immunologic
    - contains IgA, macrophages, active lymphocytes, lysozymes, lactoferrin (which inhibits *E. coli* growth in intestine)
    - lower pH promotes growth of lactobacillus in GI tract
  - parent-child bonding
  - economical, convenient

---

**Peanut Allergies in Children**

*NEJM 2015;372(9):803-813*

**Study:** 840 children identified as “at risk to peanut allergy” due to severe eczema, egg allergy, or both were split into two cohorts depending on their pre-existing sensitivity to peanut extract on skin-prick test. These two cohorts were randomized to peanut consumption or avoidance up until 60 mo of age.

**Results:** In the cohort with negative skin-prick test at start of study, prevalence of peanut allergy at 60 mo of age was 13.7% in peanut avoidance and 1.9% in the peanut consumption group. In cohort with positive skin-prick test at start of study, prevalence of peanut allergy at 60 mo of age was 35.3% in peanut avoidance and 10.8% in peanut consumption group.

**Conclusion:** Early introduction of peanuts significantly decreased prevalence of peanut allergies in children deemed “at risk to peanut allergy”.

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**Dietary Exposures and Allergy Prevention in High-Risk Infants**

*Pediatric Child Health 2013;18(10):545-549*

There is no evidence that restriction of highly allergenic foods is beneficial in the first year of life. Later introduction of peanut, fish, or egg does not prevent, and may increase the risk of developing food allergy. There is also no evidence that dietary restrictions during pregnancy or breastfeeding are protective to the child.
contraindicated if mother
  - is receiving chemotherapy or radioactive compounds
  - has HIV/AIDS, active untreated TB, herpes in breast region
  - is using >0.5 g/kg/d of alcohol or illicit drugs
  - is taking medications known to cross to breast milk
  - OCPs are not a contraindication to breastfeeding (estrogen may decrease lactation, but is not dangerous to infant)
  - MotherRisk™ Program – valuable research and counselling on reproductive risk or safety of drugs and chemicals

complications in infant
  - breastfeeding jaundice (first 1-2 wk): due to lack of maternal milk production and subsequent infant dehydration (see Jaundice, P70)
  - breast milk jaundice (0.5% of newborns, persists up to 4-6 mo): rare, not fully understood, thought to be due to substances in breast milk that inhibit conjugation of bilirubin or increase enterohepatic circulation of bilirubin, likely a biochemical problem; check bilirubin to rule out conjugated hyperbilirubinemia
  - baby presents healthy and thriving, and jaundice resolves
  - poor weight gain: consider dehydration or FIT
  - oral candidiasis (thrush): check baby’s mouth for white cheesy material that does not scrape off; treat baby with antifungal such as nystatin (Mycostatin®); can occur in breast or bottle-fed infants

### Table 6. Common Formulas Compared to Breast Milk

<table>
<thead>
<tr>
<th>Type of Nutrition</th>
<th>Indications</th>
<th>Content (as compared to breast milk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cow's Milk-Based</td>
<td>Prematurity</td>
<td>Lower whey:casein ratio</td>
</tr>
<tr>
<td>(Enfamil®, Similac® )</td>
<td>Transition into breastfeeding</td>
<td>Plant fats instead of dietary butterfat</td>
</tr>
<tr>
<td>Fortified Formula</td>
<td>Low birth weight</td>
<td>Higher calories and vitamins A, C, D, K</td>
</tr>
<tr>
<td></td>
<td>Prematurity</td>
<td>May only be used in hospital due to risk of fat-soluble vitamin toxicity</td>
</tr>
<tr>
<td>Soy Protein</td>
<td>Galactosemia</td>
<td>Corn syrup solids or sucrose in place of lactose</td>
</tr>
<tr>
<td>(Isomil® , Prosoffen®)</td>
<td>Desire for vegetarian/vegan</td>
<td></td>
</tr>
<tr>
<td>Partially Hydrolyzed Proteins</td>
<td>Delayed gastric emptying</td>
<td>Protein is 100% whey with no casein</td>
</tr>
<tr>
<td>(Good Start®)</td>
<td>Risk of cow milk protein allergy</td>
<td></td>
</tr>
<tr>
<td>Protein Hydrolysate</td>
<td>Malabsorption</td>
<td>Protein is 100% casein with no whey</td>
</tr>
<tr>
<td>(Nutramigen® , Alimentum®,</td>
<td>Food allergy</td>
<td>Corn syrup solids, sucrose, or tapioca starch instead of lactose</td>
</tr>
<tr>
<td>Pregestimil®, Portagen® )</td>
<td></td>
<td>Expensive</td>
</tr>
<tr>
<td>Amino Acid</td>
<td>Food allergy</td>
<td>Free amino acids (no protein)</td>
</tr>
<tr>
<td>(Neocate®, PurAminoTM)</td>
<td>Short gut</td>
<td>Corn syrup solids instead of lactose</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Inborn errors of metabolism</td>
<td>Various different compositions for children with galactosemia, propionic acidemia, etc.</td>
</tr>
</tbody>
</table>

*10-35% of children with cow’s milk protein allergy also have reactions to soy-based formula.

### Injury Prevention Counselling

- injuries are the leading cause of death in children >1 yr of age
- main causes: motor vehicle crashes, burns, drowning, falls, choking, infanticide

### Table 7. Injury Prevention Counselling

<table>
<thead>
<tr>
<th>0-6 mo</th>
<th>6-12 mo</th>
<th>1-2 yr</th>
<th>2-3 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not leave alone on bed, on changing table, or in tub</td>
<td>Install stair barriers</td>
<td>Never leave unattended</td>
<td>Bicycle helmet</td>
</tr>
<tr>
<td>Keep cribs raised</td>
<td>Discourage use of walkers</td>
<td>Keep pot handles turned to back of stove</td>
<td>Never leave unsupervised at home, driveway, or pool</td>
</tr>
<tr>
<td>Check water temperature before bathing</td>
<td>Avoid play areas with sharp-edged tables and corners</td>
<td>Keep pot handles turned to back of stove</td>
<td>Teach bike safety, stranger safety, and street safety</td>
</tr>
<tr>
<td>Do not hold hot liquid and infant at the same time</td>
<td>Cover electrical outlets</td>
<td>Caution with whole grapes, nuts, raw carrots, hotdogs, etc. due to choking hazard</td>
<td>Swimming lessons (&gt;4 yr), sunscreen (from 6 mo), fences around pools</td>
</tr>
<tr>
<td>Check milk temperature before feeding</td>
<td>Unplug appliances when not in use</td>
<td>No running while eating</td>
<td></td>
</tr>
<tr>
<td>Appropriate car seats are required before leaving hospital</td>
<td>Keep small objects, plastic bags, cleaning products, and medications out of reach</td>
<td>Appropriate car seats</td>
<td>Appropriate car seats</td>
</tr>
<tr>
<td>Supervise during feeding</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: This list is not exhaustive. For more details, see Rourke Baby Record (http://www.rourkebabyprecord.ca/pdf/RBR2011Enr_Eng.pdf)
Common Complaints

Breath Holding Spells

- epidemiology: 0.1-5% of healthy children 6 mo-4 yr of age, usually start during first year of life
- etiology: child is provoked (usually by anger, injury, or fear) → holds breath and becomes silent → spontaneously resolves or loses consciousness
- types
  - cyanotic (more common), usually associated with anger/frustration
  - pallid, usually associated with pain/surprise
- management
  - usually resolves spontaneously and rarely progresses to seizure
  - help child control response to frustration and avoid drawing attention to spell

Circumcision

- elective procedure
  - not covered by OHIP in Ontario, but recent evidence shows health benefits outweigh risks and justify access to procedure
  - often for religious or culture reasons
- benefits: prevention of phimosis and slightly reduced incidence of UTI, STI, balanitis, cancer of the penis
- complications (<1%): local infection, bleeding, urethral injury
- contraindications: presence of genital abnormalities (e.g. hypospadias) or known bleeding disorder

Crying/Fussing Child

- history
  - description of baseline feeding, sleeping, crying patterns
  - infectious symptoms: fever, tachypnea, rhinorrhea, ill contacts
  - feeding intolerance: gastroesophageal reflux with esophagitis, N/V, diarrhea, constipation
  - trauma
  - recent immunizations (vaccine reaction) or medications (drug reactions), including maternal drugs taken during pregnancy (neonatal withdrawal syndrome) and drugs that may be transferred via breast milk
  - inconsistent history, pattern of numerous emergency department visits, high-risk social situations all raise concern of maltreatment

Table 8. Physical Exam and Differential Diagnosis

<table>
<thead>
<tr>
<th>Organ System</th>
<th>Possible Examination Findings</th>
<th>Possible Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEENT</td>
<td>Bulging fontanelle</td>
<td>Meningitis, shaken baby syndrome, hydrocephalus</td>
</tr>
<tr>
<td></td>
<td>Blepharospasm, tearing</td>
<td>Corneal abrasion, glaucoma</td>
</tr>
<tr>
<td></td>
<td>Retinal hemorrhage</td>
<td>Shaken baby syndrome</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal infections</td>
<td>Thrush, gingivostomatitis, herpangina, otitis media</td>
</tr>
<tr>
<td>Neurological</td>
<td>Iritability or lethargy</td>
<td>Meningitis, shaken baby syndrome</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Poor perfusion</td>
<td>Sepsis, anomalous coronary artery, meningitis, myocarditis, CHF</td>
</tr>
<tr>
<td></td>
<td>Tachycardia</td>
<td>Pneumonia, CHF</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Tachypnea</td>
<td>Respiratory disease, response to pain</td>
</tr>
<tr>
<td></td>
<td>Grunting</td>
<td></td>
</tr>
<tr>
<td>Abdominal</td>
<td>Mass, empty RLQ</td>
<td>Intussusception</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>Scrotal swelling</td>
<td>Incarcerated hernia, testicular torsion</td>
</tr>
<tr>
<td></td>
<td>Penile/clitoral swelling</td>
<td>Hair tourniquet</td>
</tr>
<tr>
<td>Rectal</td>
<td>Anal fissure</td>
<td>Constipation or diarrhea</td>
</tr>
<tr>
<td></td>
<td>Hemoccult positive stool</td>
<td>Intussusception, NEC, volvulus</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Point tenderness or decreased movement</td>
<td>Fracture, syphilis, osteomyelitis, toe/finger hair tourniquet</td>
</tr>
</tbody>
</table>
Infantile Colic

- definition: unexplained paroxysms of irritability and crying for >3 h/d, >3 d/wk for >3 wk in an otherwise healthy, well-fed baby (rule of 3s)
- epidemiology: 10% of infants; usual onset 10 d to 3 mo of age with peak at 6-8 wk
- etiology: lag in development of normal peristaltic movement in gastrointestinal tract; other theories suggest a lack of self-soothing mechanisms or extreme of normal
- management
  - parental relief, rest, and reassurance
  - hold baby, soother, car ride, music, vacuum, check diaper
  - medications (Ovol® drops, gripe water) have no proven benefit, some evidence for probiotics
  - if breastfeeding, elimination of cow’s milk protein from mother’s diet (effective in very small percentage of cases)
  - try casein hydrolysate formula (Nutramigen®)
  - time – all resolve, most in the first 2-3 mo of life

Dentition and Caries

Dentition
- primary dentition (20 teeth)
  - first tooth at 5-9 mo (lower incisor), then 1/mo
  - 6-8 central teeth by 1 yr
  - assessment by dentist 6 mo after eruption of first tooth and certainly by 1 yr of age (Grade B recommendation)
- secondary dentition (32 teeth)
  - first adult tooth is 1st molar at 6 yr, then lower incisors

Caries
- milk caries: decay of superior front teeth and back molars in first 4 yr of life
- cause: often due to prolonged feeding (e.g. put to bed with bottle, prolonged breastfeeding)
- prevention
  - no bottle at bedtime, clean teeth after last feed
  - minimize juice and sweetened pacifier
  - clean teeth with soft damp cloth or toothbrush and water
  - water fluoridation

Enuresis

Definition
- involuntary urinary incontinence by day and/or night in child >5 yr

General Approach
- should be evaluated if dysuria, change in colour, odour, stream, secondary or diurnal, change in gait, stool incontinence

Primary Nocturnal Enuresis
- definition: involuntary loss of urine at night, bladder control has never been attained
- epidemiology: boys > girls; 10% of 6 yr olds, 3% of 12 yr olds, 1% of 18 yr olds
- etiology: developmental disorder or maturational lag in bladder control while asleep
- management
  - time and reassurance (~20% resolve spontaneously each yr)
  - behaviour modification (limiting fluids, voiding prior to sleep), bladder retention exercises, scheduled toileting overnight has limited effectiveness
  - conditioning: “wet” alarm wakes child upon voiding (70% success rate)
  - medications (considered second line therapy, may be used for sleepovers/camp): DDAVP oral tablets (high relapse rate, costly), imipramine (Tofranil®) (rarely used, lethal if overdose, cholinergic side effects)

Secondary Enuresis
- definition: involuntary loss of urine at night, develops after child has sustained period of bladder control (>6 mo)
- etiology: inorganic regression due to stress or anxiety (e.g. birth of sibling, significant loss, family discord), focused on other activities, secondary to organic disease (UTI, DM, DI, neurogenic bladder, CP, seizures, pinworms)
- management: treat underlying cause

Antidiuretic Hormone Regulation in Primary Nocturnal Enuresis
Arch Dis Child 1995;73(6):508-11
Treatment of primary nocturnal enuresis using DDAVP is based upon the hypothesis that ADH secretion is insufficient at night. The known efficacy of the treatment on the one hand, and persisting doubts about its theoretical basis on the other, formed the background of the present study. Ten children (mean age 10.5 yr) with primary nocturnal enuresis were compared with a corresponding control group of eight patients. Diurnal and nocturnal urine production, ADH secretion, and plasma osmolality were determined. No differences between the two groups were found for urine production, ADH levels during day and night, or plasma osmolality. However, in order to regulate plasma osmolality the enuretic children required a markedly greater output of ADH 2.87 pg/millimol/kg compared with 0.56 in the controls (p < 0.01). The results are consistent with the established fact that ADH secretion is a function of plasma osmolality, and they contradict the hypothesis that urine production is increased at night in enuretics because of lower ADH secretion.
Diurnal Enuresis
• definition: daytime wetting (60-80% also wet at night)
• etiology: micturition deferral (holding urine until last minute) due to psychosocial stressor (e.g. shy), structural anomalies (e.g. ectopic ureteral site, neurogenic bladder), UTI, constipation, CNS disorders, DM
• management: treat underlying cause, behavioural (scheduled toileting, double voiding, good bowel program), pharmacotherapy

Encopresis
• definition: fecal incontinence in a child >4 yr old, at least once per mo for 3 mo
• prevalence: 1-1.5% of school-aged children (rare in adolescence); M:F = 6:1 in school-aged children
• causes: chronic constipation (retentive encopresis), Hirschsprung disease, hypothyroidism, hypercalcemia, spinal cord lesions, anorectal malformations, bowel obstruction

Retentive Encopresis
• definition: child holds bowel movement, develops constipation, leading to fecal impaction and seepage of soft or liquid stool (overflow incontinence)
• etiology
  • physical: painful stooling often secondary to constipation
  • emotional: disturbed parent-child relationship, coercive toilet training, social stressors
• clinical presentation
  • history
    • crosses legs or stands on toes to resist urge to defecate
    • distressed by symptoms, soiling of clothes
    • toilet training coercive or lacking in motivation
    • may show oppositional behaviour
    • abdominal pain
  • physical exam
    • digital rectal exam: large fecal mass in rectal vault
    • anal fissures (result from passage of hard stools)
    • palpable stool in LLQ
• management
  • complete clean-out of bowel: PEG 3350 given orally is most effective, enemas and suppositories may be second line therapies, but these are invasive and often less effective
  • maintenance of regular bowel movements (see Pediatric Gastroenterology, Constipation Treatment, P38)
  • assessment and guidance regarding psychosocial stressors
  • behavioural modification
• complications: recurrence, toxic megacolon (requires >3-12 mo to treat), bowel perforation

Toilet Training
• 90% of children attain bladder control before bowel control
• generally, females train earlier than males
• 25% by 2 yr (in North America), 98% by 3 yr have daytime bladder control
• signs of toilet readiness
  • ambulating independently, stable on potty, desire to be independent or to please caregivers (i.e. motivation), sufficient expressive and receptive language skills (2-step command level), can stay dry for several hours (large enough bladder), can recognize need to go, able to remove clothing

Failure to Thrive
• definition
  • weight <3rd percentile, falls across two major percentile curves, or <80% of expected weight for height and age
  • inadequate caloric intake most common factor in poor weight gain
  • may have other nutritional deficiencies (e.g. protein, iron, vitamin D)
  • factors affecting physical growth: genetics, intrauterine factors, internal time clock, nutrition, endocrine hormones, chronic infections/diseases, psychosocial factors
• clinical presentation
  • history
    • nutritional intake
    • current symptoms
    • past illnesses

**Energy Requirements**
- 0-10 kg: 100 kcal/kg/d
- 10-20 kg: 1,000 kcal + 50 kcal/kg/d for each kg >10
- >20 kg: 1,500 kcal + 20 kcal/kg/d for each kg >20
• family history: growth, puberty, parental height and weight including mid-parental height
• psychosocial history
• physical exam
• growth parameters, plotted: height, weight, head circumference, arm span
• vital signs
• complete head to toe exam
• dysmorphic features or evidence of chronic disease
• upper to lower segment ratio
• sexual maturity staging
• signs of maltreatment or neglect
• investigations (as indicated by clinical presentation)
  • CBC, blood smear, electrolytes, T4, TSH
• bone age x-ray
• chromosomes/karyotype
• chronic illness: chest (CXR, sweat Cl\(^-\)), cardiac (CXR, ECG, Echo), GI (celiac screen, inflammatory markers, malabsorption), renal (urinalysis), liver (enzymes, albumin)

Table 9. Failure to Thrive Patterns

<table>
<thead>
<tr>
<th>Growth Parameters</th>
<th>Suggestive Abnormality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased Wt</td>
<td>Normal Ht Normal HC</td>
</tr>
<tr>
<td></td>
<td>Caloric insufficiency Decreased intake</td>
</tr>
<tr>
<td></td>
<td>Hypermetabolic state Increased losses</td>
</tr>
<tr>
<td>Decreased Wt Decreased Ht</td>
<td>Normal HC</td>
</tr>
<tr>
<td></td>
<td>Structural dystrophies Endocrine disorder</td>
</tr>
<tr>
<td></td>
<td>Constitutional growth delay (BA &lt; CA) Familial short stature (BA = CA)</td>
</tr>
<tr>
<td>Decreased Wt Decreased Ht Decreased HC</td>
<td>Intrauterine insult Genetic abnormality</td>
</tr>
</tbody>
</table>

BA = bone age; CA = chronological age; HC = head circumference; Ht = height; Wt = weight

Non-Organic FTT (90%)
• most common cause of FTT
• results from complex factors in parent-child relationship
  • dietary intake, knowledge about feeding, improper mixing of formula, economic factors
  • feeding environment
  • parent-child interaction, attachment
  • child behaviours, hunger/satiety cues
  • social factors: stress, poverty
• management
  • most as outpatient using multidisciplinary approach: primary care physician, dietitian, psychologist, social work, CAS
  • medical: oromotor problems, iron-deficiency anemia, gastroesophageal reflux
  • nutritional: educate about age-appropriate foods, calorie boosting, mealtime schedules and environment; goal to reach 90-110% IBW, correct nutritional deficiencies, and promote catch-up growth/development
  • behavioural: positive reinforcement, mealtime environment

Organic FTT (10%)
• inadequate intake: non-organic, vomiting, oromotor dysfunction, anorexia
• excessive consumption: CHD, CF, hyperthyroidism
• abnormal utilization: inborn errors of metabolism
• excessive output: IBD, celiac, malabsorption
• management: treat specific cause

Energy Requirements
• see Nutrition, P6

Obesity
• definition: BMI >95th percentile for age and height
• risk factors: genetic predisposition (e.g. both parents obese – 80% chance of obese child)
• etiology: organic causes are rare (<5%), but may include Prader-Willi, Carpenter, Turner, Cushing syndromes, hypothyroidism
• complications: association with HTN, dyslipidemia, slipped capital femoral epiphysis, type 2 DM, asthma, obstructive sleep apnea, gynecostasia, polycystic ovarian disease, early menarche, irregular menses, psychological trauma (e.g. bullying, decreased self-esteem, unhealthy coping mechanisms, depression)
• childhood obesity often persists into adulthood
• management
  • encouragement and reassurance; engagement of entire family
  • diet: qualitative changes (do not encourage weight loss, but allow for linear growth to catch up with weight), special diets used by adults and very low calorie diets are not encouraged
- behaviour modification: increase activity, change eating habits/meal patterns
- education: multidisciplinary approach, dietitian, counselling
- surgery and pharmacotherapy are rarely used in children
- increase physical activity (30 min/day), reduce screen time

**Poison Prevention**

- keep all types of medicines, vitamins, and chemicals locked up in a secure container
- potentially dangerous: medications, illicit drugs, drain cleaners, furniture polish, insecticides, cosmetics, nail polish remover, automotive products
- do not store any chemicals in juice, soft drink, or water bottles
- always read labels before administering medicine to ensure correct medication drug and dose and/or speak with a pharmacist or healthcare provider

**Rashes**

<table>
<thead>
<tr>
<th>Type of Rash</th>
<th>Differential</th>
<th>Appearance</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diaper Dermatitis</td>
<td>Irritant contact dermatitis</td>
<td>Shiny, red macules/patches, no skin fold involvement</td>
<td>Eliminate direct skin contact with urine and feces, allow periods of rest without a diaper, frequent diaper changes, topical barriers (petrolatum, zinc oxide or paste), short-term low-potency topical corticosteroids (severe cases)</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>Yellow, greasy macules/plaques on erythema, scales</td>
<td>Short-term, low-potency topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td>Candidal dermatitis</td>
<td>Erythematous macerated papules/plaques, satellite lesions, involvement of skin folds</td>
<td>Antifungal agents</td>
<td></td>
</tr>
<tr>
<td>Other Dermatitis</td>
<td>Atopic dermatitis</td>
<td>Erythematous, papules/plaques, oozing, excoriation, lichenification, classic areas of involvement</td>
<td>Eliminate exacerbating factors, maintain skin hydration, corticosteroids, topical calcineurin inhibitor, daily baths</td>
</tr>
<tr>
<td>Nummular dermatitis</td>
<td>Annular erythematous plaques, oozing, crustling</td>
<td>Avoid irritant if identified, potent topical steroid in emollient base, short-term systemic steroids ± antibiotics (severe)</td>
<td></td>
</tr>
<tr>
<td>Allergic contact dermatitis</td>
<td>Red papules/plaques/vesicles/bullae, only in area of allergen</td>
<td>Mild: soothing lotion (e.g. calamine lotion) Moderate: low-to-intermediate potency topical corticosteroids Severe: systemic corticosteroids and antihistamine</td>
<td></td>
</tr>
<tr>
<td>Irritant contact dermatitis</td>
<td>Morphology depends on irritant</td>
<td>Avoid skin contact</td>
<td></td>
</tr>
<tr>
<td>Dyshidrotic dermatitis</td>
<td>Papulovesicular, cracking/fissuring, hands and feet (&quot;tapioca pudding&quot;)</td>
<td>Mild/moderate: medium/potent topical corticosteroids Severe: systemic corticosteroids, local PUVA or UVA treatments</td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>Scabies</td>
<td>Polymorphic (red excoriated papules/nodules, burrows), in web spaces/folds, very pruritic</td>
<td>Permethrin (Nix®) 5% cream for patient and family (2 applications, 1 wk apart)</td>
</tr>
<tr>
<td>Impetigo</td>
<td>Honey-coloured crusts or superficial bullae</td>
<td>Oral antibiotics (e.g. cephalaxin/erythromycin) Topical if mild: fucidic acid or mupirocin cream</td>
<td></td>
</tr>
<tr>
<td>Tinea corporis</td>
<td>Round erythematous plaques, central clearing and scaly border</td>
<td>Topical anti-fungal for skin, systemic anti-fungals for nails/head</td>
<td></td>
</tr>
</tbody>
</table>

**Pediatric Exanthems** (see Infectious Pediatric Exanthems, P56)

**Drug Reactions** (see Dermatology, D22)

**Acne** (see Dermatology, D11)
Sleep Disturbances

Types of Sleep Disturbances

• insufficient sleep quantity
  ▪ difficulty falling asleep (e.g. limit setting sleep disorder)
  ▪ preschool and older children
  ▪ bedtime resistance
  ▪ due to caregiver’s inability to set consistent bedtime rules and routines
  ▪ often exacerbated by child’s oppositional behaviours

• poor sleep quality
  ▪ frequent arousals (e.g. sleep-onset association disorder)
  ▪ infants and toddlers
  ▪ child learns to fall asleep only under certain conditions or associations (e.g. with parent, held, rocked or fed, with light on, in front of television), and loses ability to self-soothe
  ▪ during the normal brief arousal periods of sleep (q90-120 min), child cannot fall back asleep because same conditions are not present

• obstructive sleep apnea
  ▪ epidemiology: 1-5% of preschool aged children, more common in African American children
  ▪ definition: partial or intermittent complete airway obstruction during sleep causing disrupted ventilation and sleep pattern
  ▪ features: snoring/gasping/noisy breathing during sleep and irritable/tired/hyperactive during the day
  ▪ sequelae: cardiovascular (HTN/LV remodeling due to sympathetic activation), growth, cognitive, and behavioural deficits
  ▪ risk factors: adenotonsillar hypertrophy, obesity
  ▪ management: watchful waiting, weight reduction, airway pressure devices, or surgery depending on the cause
  ▪ adenotonsillectomy does not improve executive function or attention but reduces symptoms and improves behaviour, quality of life, and polysomnographic findings

• parasomnias
  ▪ episodic nocturnal behaviours (e.g. sleepwalking, sleep terrors, nightmares)
  ▪ often involves cognitive disorientation and autonomic/skeletal muscle disturbance

Management of Sleep Disturbances

• set strict bedtimes and “wind-down” routines
• do not send child to bed hungry
• positive reinforcement for: limit setting sleep disorder
• always sleep in own bed, in a dark, quiet, and comfortable room
• do not use bedroom for timeouts
• systematic ignoring and gradual extinction for: sleep-onset association disorder

Nightmares

• epidemiology: common in boys, 4-7 yr old
• associated with REM sleep (anytime during night)
• features: upon awakening, child is alert and clearly recalls frightening dream ± associated with daytime stress/anxiety
• management: reassurance

Night Terrors

• epidemiology: 15% of children have occasional episodes
• abrupt sitting up, eyes open, screaming
• clinical features: occurs in early hours of sleep, stage 4 of sleep; signs of panic and autonomic arousal, no memory of event, inconsolable, stress/anxiety can aggravate them
• course: remits spontaneously at puberty
• management: reassurance for parents, ensure child is safe (e.g. if sleepwalks)

Sudden Infant Death Syndrome

Definition

• sudden and unexpected death of an infant <12 mo of age in which the cause of death cannot be found by history, examination, or a thorough postmortem and death scene investigation

Epidemiology

• 0.5/1,000 (leading cause of death between 1-12 mo of age); M:F = 3:2
• more common in children placed in prone position
• in full term infants, peak incidence is 2-4 mo, 95% of cases occur by 6 mo
• increase in deaths during peak RSV season
• most deaths occur between midnight and 8 AM
Risk Factors
- prematurity, smoking in household, socially disadvantaged, higher incidence in Aboriginals and African Americans
- risk of SIDS is increased 3-5x in siblings of infants who have died of SIDS
- bedsharing: sleeping on a sofa, sleeping with an infant after consumption of alcohol/street drugs or extreme fatigue, infant sleeping with someone other than primary caregiver

Prevention
- “Back to Sleep, Front to Play” (place infant on back when sleeping)
- allow supervised play time daily in prone position (“tummy time”)
- alarms, monitors not recommended – increase anxiety, do not prevent life-threatening events
- avoid overheating and overdressing
- appropriate infant bedding (firm mattress; avoid loose bedding, pillows, stuffed animals, and crib bumper pads)
- no smoking
- pacifiers appear to have a protective effect; do not reinsert if falls out during sleep

Child Abuse and Neglect

Definition
- an act of commission (physical, sexual, or psychological abuse) or omission (neglect) by a caregiver that harms a child

Legal Duty to Report
- upon reasonable grounds to suspect abuse and/or neglect, physicians are required by legislation to contact the CAS to personally disclose all information relevant to the child safety concern
- duty to report overrides patient confidentiality; physician is protected against liability

Ongoing Duty to Report
- if there are additional reasonable grounds to suspect abuse and/or neglect, a further report to the CAS must be made

Risk Factors
- environmental factors: social isolation, poverty, domestic violence
- caregiver factors: personal history of abuse, psychiatric illness, substance abuse, single parent family, poor social and vocational skills, below average intelligence
- child factors: difficult temperament, disability, special needs (e.g. developmental delay), premature

Physical Abuse

History
- history that is not compatible with physical findings, or history not reproducible
- delay in seeking medical attention that is unexplained by other factors

Physical Exam
- physical findings not explained by underlying medical condition
- growth parameters (weight, height, head circumference)
- recurrent or multiple injuries not explained by accidental injury or child’s development level
- patterned skin injuries: belt buckle, hand prints, burns that do not match provided history
- injury location: bruises on areas with abundant soft-tissue cushioning, such as abdomen, buttocks, genitalia, fleshy part of cheek; bruises on ears; posterior rib/metaphyseal/scapular/vertebral/ternal fractures (more suspicious for non-accidental injuries); immersion burns (e.g. hot water)
- altered mental status: head injury, poisoning
- head trauma is the leading cause of death in child maltreatment (e.g. acceleration-deceleration forces [shaking], direct force application [blow or impact])

Investigations
- document all injuries on a body diagram: type, location, size, shape, colour, pattern
- photography of skin injuries is ideal (police or hospital photography preferred; do not use physician’s personal camera)
- rule out medical causes of bruising/fracture with appropriate investigations:
  - if fractures evident: Ca\(^{2+}\), Mg\(^{2+}\), PO\(_4\)^{3-}, ALP, PTH, Vitamin D, renal function, and bone density
  - if bruising present: CBC, INR, PTT, von Willebrand factor, factors VII/IX/X/XIII
  - screen for abdominal trauma (transaminases and amylase): if increased, abdo CT recommended
  - skeletal survey in children <2 yr
    - bone scan can be beneficial for assessing rib fractures (not helpful for skull or metaphyseal region due to active bone growth) – consider bone scan if equivocal findings on initial skeletal survey
    - dilated eye examination by pediatric ophthalmologist to rule out retinal hemorrhage
    - be aware of “red herrings” (e.g. Mongolian blue spots vs. bruises)
  - neuroimaging: CT and/or MRI

Apparent Life-Threatening Events
A group of conditions often marked by an episode of apnea, cyanosis, change in tone, or change in mental status occurring in a child, where an observer fears the child may be dying. There is no clear connection between most ALTEs and SIDS. Evaluating for a cause of the ALTE (e.g. infection, cardiac, neurologic) is guided by history, physical exam, and period of observation
Sexual Abuse

**Epidemiology**
- peak ages at 2-6 yr and 12-16 yr
- most perpetrators are male and known to child
  - in decreasing order: family member, non-relative known to victim, stranger

**History**
- diagnosis usually depends on child disclosing to someone or forensic interview done by a trained individual
- psychosocial: specific or generalized fears, depression, nightmares, social withdrawal, lack of trust, low self-esteem, school failure, sexually aggressive behaviour, advanced sexual knowledge, sexual preoccupation or play

**Physical Exam**
- recurrent UTIs, pregnancy, STIs, vaginitis, vaginal bleeding, pain, genital injury, enuresis

**Investigations**
- depend on presentation, age, sex, and pubertal development of child
  - sexual assault examination kit within 24 h if prepubertal, within 72 h if pubertal
  - rule out STI, UTI, pregnancy (consider STI prophylaxis or emergency contraception)
  - rule out other injuries (vaginal/anal/oral penetration, fractures, head trauma)

Neglect

**History**
- from child and each caregiver separately (if possible)

**Physical Exam**
- head to toe (do not force), growth parameters, nutrition status
- dental care
- emotional state

**Investigations**
- blood tests to rule out medical conditions (e.g. thrombocytopenia or coagulopathy)

Management of Physical Abuse, Child Abuse, and Neglect
- report all suspicions to CAS; request emergency visit if imminent risk to child or any siblings in the home
- acute medical care: hospitalize for medical evaluation or treatment of injuries if indicated
- arrange consultation to social work and appropriate follow-up
- may need to discharge child directly to CAS or to responsible guardian under CAS supervision

Adolescent Medicine

Adolescent History (HEEADSSS)
- tailor your history according to the clinical context

**Home:** Who do you live with? What kind of place do you live in?

**Education/Employment:** What grade are you in? What are your favourite subjects? What was your average on your last report card?

**Eating:** Tell me about your meals/snacks in a typical day. Have you ever gone on a diet? (see Eating Disorders, Psychiatry, PS32)

**Activities:** What do you do after school? On the weekends? How much time do you spend on the computer/watching TV every day? Do you use social media (i.e. Facebook, Twitter, Instagram, etc.)?

**Drugs:** Which seems to be more popular at your school, alcohol or drugs? How often do you drink/smoke marijuana/take other drugs? Do you smoke cigarettes? When you drink, do you usually get drunk? Have you ever passed out or not been able to remember what happened while you were drinking? Has anything bad ever happened to you while you were drunk or stoned? (see Substance Abuse, Psychiatry, PS23)

**Sexuality:** Are you romantically interested in anyone? When you think about having sex with someone, do you think about girls, boys, or both? Have you ever had sex with anyone? Whether the answer is yes or no, the next question is: What activities would you include in the term ‘having sex’? What do you do to prevent getting a STI/getting pregnant/getting someone pregnant? Has anyone ever given you money, drugs, or other stuff in exchange for sex? (see Sexually Transmitted Infections, Gynecology, GY25)

Presentation of Neglect
- FTT, developmental delay
- Inadequate or dirty clothing, poor hygiene
- Child exhibits poor attachment to parents, no stranger anxiety

Rates of drug use in high school students who have used in the past year: alcohol (58.2%), cannabis (25.6%), tobacco (11.7%)

Date rape comprises 80% of sexual assault in teenagers
Suicidality/Depression: On a scale of 1 to 10, where 1 is so sad that you might kill yourself and 10 is the happiest you could be, where are you most days? Is there a difference between school days and the weekend? Have you ever thought seriously about suicide? Did you make a plan? (see Depression/Suicide, Psychiatry PS9, PS4)

Safety/Violence: Do you ever get into a car with a driver who has been drinking? Do you always wear a seatbelt/bicycle helmet? Are you being bullied at school? Has anyone ever touched you in an unwanted way?

See Normal and Abnormal Pubertal Development, P31

Cardiology

Congenital Heart Disease

Prenatal Circulation

Embryologic Development
- most critical period of fetal heart development is between 3-8 wk gestation
- single heart tube grows rapidly, forcing it to bend back upon itself and assume the shape of a four chambered heart; insults at this time are most likely to lead to CHD

Before Birth
- fetal lungs are bypassed by flow through fetal shunts
  - ductus arteriosus: connection between pulmonary artery and aorta
  - foramen ovale: connection between right and left atria
  - ductus venosus: connection between umbilical vein and inferior vena cava

At Birth
- with first breath, lungs open up → pulmonary resistance decreases → pulmonic blood flow increases
- separation of low resistance placenta → systemic circulation becomes a high resistance system → ductus venosus closure
- increased pulmonic flow → increased left atrial pressures → foramen ovale closure
- increased oxygen concentration in blood after first breath → decreased prostaglandins → ductus arteriosus closure
- closure of fetal shunts and changes in vascular resistance → infant circulation assumes normal adult flow

Prevalence of depression: 1-2% in pre-pubertal children and 6-8% in adolescents
Epidemiology
• 8/1,000 live births have CHD, which may present as a heart murmur, heart failure, or cyanosis; VSD is the most common lesion

Investigations
• Echo, ECG, CXR
• pre and postductal oxygen saturations, 4 limb BPs, hyperoxia test

CYANOTIC VS. ACYANOTIC CONGENITAL HEART DISEASE
• cyanosis: blue mucous membranes, nail beds, and skin secondary to an absolute concentration of deoxygenated hemoglobin of at least 30 g/dL.
• acyanotic heart disease (i.e. L to R shunt, obstruction occurring beyond lungs): blood passes through pulmonic circulation → oxygenation takes place → low levels of deoxygenated blood in systemic circulation → no cyanosis
• cyanotic heart disease (i.e. R to L shunt): blood bypasses the lungs → no oxygenation occurs → high levels of deoxygenated hemoglobin enters the systemic circulation → cyanosis

Figure 2. Common congenital heart diseases

Acyanotic Congenital Heart Disease

1. LEFT-TO-RIGHT SHUNT LESIONS
• extra blood is displaced through a communication from the left to the right side of the heart → increased pulmonary blood flow → increased pulmonary pressures
• shunt volume is dependent upon three factors: (1) size of defect, (2) pressure gradient between chambers or vessels, and (3) peripheral outflow resistance
• untreated shunts can result in pulmonary vascular disease, left ventricular dilatation and dysfunction, right ventricular HTN and RVH, and ultimately R to L shunts

Atrial Septal Defect
• 3 types: ostium primum (common in DS), ostium secundum (most common type, 50-70%), sinus venosus (defect located at entry of superior vena cava into right atrium)
• epidemiology: 6-8% of congenital heart lesions
• natural history
  ▪ 80-100% spontaneous closure rate if ASD diameter <8 mm
  ▪ if remains patent, CHF and pulmonary HTN can develop in adult life
• clinical presentation
  ▪ history: often asymptomatic in childhood
  ▪ physical exam: grade 2-3/6 pulmonic outflow murmur, widely split and fixed S2
  ▪ children with large ASDs may have signs of heart failure (tachypnea, FTT, hepatomegaly, pulmonary rales/retractions)
• investigations
  ▪ ECG: RAD, mild RVH, RBBB
  ▪ CXR: increased pulmonary vasculature, cardiac enlargement
  ▪ Echo: test of choice
• management: elective surgical or catheter closure between 2-5 yr of age

Ventricular Septal Defect
• most common congenital heart defect (30-50%)
• small VSD (majority)
  ▪ clinical presentation
    ▪ history: asymptomatic, normal growth and development
    ▪ physical exam: early systolic to holosystolic murmur, best heard at LLSB, thrill
investigations: ECG and CXR are normal; Echo to confirm diagnosis
management: most close spontaneously

- moderate-to-large VSD
  epidemiology: CHF by 2 mo; late secondary pulmonary HTN if left untreated
  clinical presentation
    - history: delayed growth, decreased exercise tolerance, recurrent URTIs or “asthma” episodes
    - physical exam: holosystolic murmur at LLSB, mid-diastolic rumble at apex, size of VSD is inversely related to intensity of murmur
  investigations
    - ECG: LVH, LAH, RVH
    - CXR: increased pulmonary vasculature, cardiomegaly, CHF
    - Echo: diagnostic
  management: treatment of CHF and surgical closure by 1 yr old

Patent Ductus Arteriosus
- patent vessel between descending aorta and left pulmonary artery (normally, functional closure within first 15 h of life, anatomical closure within first days of life)
- epidemiology
  - 5-10% of all congenital heart defects
  - delayed closure of ductus is common in premature infants (1/3 of infants <1,750 g); this is different from PDA in term infants
  - natural history: spontaneous closure common in premature infants, less common in term infants
- clinical presentation
  - history: asymptomatic, or have apneic or bradycardic spells, poor feeding, accessory muscle use, CHF
  - physical exam: tachycardia, bounding pulses, hyperactive precordium, wide pulse pressure, continuous “machinery” murmur best heard at left infraclavicular area
- investigations
  - ECG: may show left atrial enlargement, LVH, RVH
  - CXR: normal to mildly enlarged heart, increased pulmonary vasculature, prominent pulmonary artery
  - Echo: diagnostic
- management
  - indomethacin (Indocid®): antagonizes prostaglandin E2, which maintains ductus arteriosus patency; only effective in premature infants
  - catheter or surgical closure if PDA causes respiratory compromise, FTT, or persists beyond 3rd mo of life

2. OBSTRUCTIVE LESIONS
- present with decreased urine output, pallor, cool extremities and poor pulses, shock, or sudden collapse

Coarctation of the Aorta
- definition: narrowing of aorta (almost always at the level of the ductus arteriosus)
- epidemiology: commonly associated with bicuspid aortic valve (50%); Turner syndrome (35%)
- clinical presentation
  - history: often asymptomatic
  - physical exam
    - blood pressure discrepancy between upper and lower extremities (increased suspicion/severity if >20 mmHg difference)
    - diminished or delayed femoral pulses relative to brachial (i.e. brachial-femoral delay)
    - possible systolic murmur with late peak at apex, left axilla, and left back
    - if severe, presents with shock in the neonatal period when the ductus arteriosis closes
- investigations: ECG shows RVH early in infancy, LVH later in childhood; Echo or MRI for diagnosis
- prognosis: can be complicated by HTN; if associated with other lesions (e.g. PDA, VSD) can lead to CHF
- management: give prostaglandins to keep ductus arteriosus patent for stabilization and perform surgical correction in neonates; for older infants and children balloon arterioplasty may be an alternative to surgical correction

Aortic Stenosis
- 4 types: valvular (75%), subvalvular (20%), supravalvular, and idiopathic hypertrophic subaortic stenosis (5%)
- clinical presentation
  - history: often asymptomatic, but may be associated with CHF, exertional chest pain, syncope, or sudden death
  - physical exam: SEM at RUSB with aortic ejection click at the apex (only for valvular stenosis)
- investigations: Echo for diagnosis
- management: valvular stenosis is usually treated with balloon valvuloplasty, patients with subvalvular or supravalvular stenosis require surgical repair, exercise restriction required

Moderate-to-Large VSD
- Size of VSD is inversely related to intensity of murmur

Physical Exam for PDA
- (in term infant)
  - Heavy “machinery” murmur
  - Wide pulse pressure
  - Hyperactive precordium
  - Big bounding pulse

Figure 3. Patent ductus arteriosus

Figure 4. Coarctation of the aorta

Figure 4. Coarctation of the aorta
Pulmonary Stenosis
- 3 types: valvular (90%), subvalvular, or supravalvular
- definition of critical pulmonary stenosis: inadequate pulmonary blood flow, dependent on ductus for oxygenation, progressive hypoxia and cyanosis
- natural history: may be part of other congenital heart lesions (e.g. Tetralogy of Fallot) or in association with syndromes (e.g. congenital rubella, Noonan syndrome)
- clinical presentation
  - history: spectrum from asymptomatic to CHF
  - physical exam: wide split S2 on expiration, SEM at LUSB, pulmonary ejection click (for valvular lesions)
- investigations
  - ECG: RVH
  - CXR: post-stenotic dilation of the main pulmonary artery
  - Echo: diagnostic
- management: surgical repair if critically ill or if symptomatic in older infants/children

Cyanotic Congenital Heart Disease
- systemic venous return re-enters systemic circulation directly
- most prominent feature is cyanosis (O₂ sat <75%)
- hyperoxic test differentiates between cardiac and other causes of cyanosis
  - obtain preductal, right radial ABG in room air, then repeat after the child inspires 100% O₂
  - if PaO₂ improves to greater than 150 mmHg, cyanosis less likely cardiac in origin
- pre-ductal and post-ductal pulse oximetry
  - >5% difference suggests R to L shunt

1. RIGHT-TO-LEFT SHUNT LESIONS

Tetralogy of Fallot
- epidemiology: 10% of all CHD, most common cyanotic heart defect diagnosed beyond infancy with peak incidence at 2-4 mo of age
- pathophysiology
  - embryological defect due to anterior and superior deviation of the outlet septum leading to: VSD, RVOTO (i.e. pulmonary stenosis), over-riding aorta, and RVH
  - infants may initially have a L → R shunt (therefore no cyanosis); however, RVOTO is progressive, leading to increasing R → L shunting with hypoxemia and cyanosis
  - degree of RVOTO determines the direction and degree of shunt and, therefore, the extent of clinical cyanosis and degree of RVH
- clinical presentation
  - history: hypoxic “tet” spells
    - during exertional states (crying, exercise) the increasing pulmonary vascular resistance and decrease in systemic resistance causes an increase in right-to-left shunting
    - clinical features include paroxysms of rapid and deep breathing, irritability and crying, increasing cyanosis, decreased intensity of murmur (decreased flow across RVOTO)
  - if severe, can lead to decreased level of consciousness, seizures, death
  - physical exam
    - single loud S2 due to severe pulmonary stenosis (i.e. RVOTO), SEM at LSB
- investigations
  - ECG: RAD, RVH
  - CXR: boot-shaped heart, decreased pulmonary vasculature, right aortic arch (in 20%)
  - Echo: diagnostic
- management of spells: O₂, knee-chest position, fluid bolus, morphine sulfate, propranolol
- treatment: surgical repair at 4-6 mo of age; earlier if marked cyanosis or “tet” spells

2. OTHER CYANOTIC CONGENITAL HEART DISEASES

Transposition of the Great Arteries (TGA)
- epidemiology: 3-5% of all congenital cardiac lesions, most common cyanotic CHD in neonates
- pathophysiology: parallel pulmonary and systemic circulations
  - systemic: body → RA → RV → aorta → body
  - pulmonary: lungs → LA → LV → pulmonary artery → lungs
  - survival is dependent on mixing through PDA, ASD, or VSD
- physical exam
  - neonates: ductus arteriosus closure causes rapidly progressive severe hypoxemia unresponsive to oxygen therapy, acidosis, and death
  - VSD present: cyanosis is not prominent; CHF within first weeks of life
  - VSD absent: no murmur

Figures: Tetralogy of Fallot, Transposition of the great arteries
• investigations
  ᵉ ECG: RAD, RVH, or may be normal
  ᵉ CXR: egg-shaped heart with narrow mediastinum (“egg on a string”)
  ᵉ Echo: diagnostic

• management
  ᵉ symptomatic neonates: prostaglandin E1 infusion to keep ductus open until balloon atrial septostomy
  ᵉ surgical repair: arterial switch performed in the first two weeks in those without a VSD while LV muscle is still strong

Total Anomalous Pulmonary Venous Return
• epidemiology: 1-2% of CHD
• pathophysiology
  ᵇ all pulmonary veins drain into right-sided circulation (systemic veins, RA)
  ᵇ no direct oxygenated pulmonary venous return to left atrium
  ᵇ often associated with obstruction at connection sites
  ᵇ ASD must be present for oxygenated blood to shunt into the LA and systemic circulation
• management: surgical repair in all cases and required urgently for severe cyanosis

Truncus Arteriosus
• pathophysiology
  ᵇ single great vessel gives rise to the aorta, pulmonary, and coronary arteries
  ᵇ truncal valve overlies a large VSD
  ᵇ potential for coronary ischemia with fall in pulmonary vascular resistance
• management: surgical repair within first 6 wk of life

Hypoplastic Left Heart Syndrome
• epidemiology: 1-3% of CHD; most common cause of death from CHD in first month of life
• pathophysiology
  ᵇ LV hypoplasia may include atretic or stenotic mitral and/or aortic valve, small ascending aorta, and coarctation of the aorta with resultant systemic hypoperfusion
  ᵇ systemic circulation is dependent on ductus patency; upon closure of the ductus, infant presents with circulatory shock and metabolic acidosis
• management
  ᵇ intubate and correct metabolic acidosis
  ᵇ IV infusion of prostaglandin E1 to keep ductus open
  ᵇ surgical palliation (overall survival 50% to late childhood) or heart transplant

Congestive Heart Failure
• see Cardiology and Cardiac Surgery, C36

Etiology
• CHD
• cardiomyopathy (primary or secondary)
• high output circulatory states (e.g. anemia, AVMs, cor pulmonale, hyperthyroidism)
• non-cardiac (e.g. sepsis, renal failure)
• pressure overload (e.g. aortic stenosis/co-arctation, pulmonary stenosis, HTN)
• volume overload (e.g. L to R shunt, valve insufficiency)

History
• infant: feeding difficulties, early fatigability, diaphoresis while sleeping or eating, respiratory distress, lethargy, FTT
• child: decreased exercise tolerance, fatigue, decreased appetite, respiratory distress, frequent URTIs or “asthma” episodes
• orthopnea, paroxysmal nocturnal dyspnea, pedal/dependent edema are all uncommon in children

Physical Findings
• 4 key features: tachycardia, tachypnea, cardiomegaly, hepatomegaly
• FTT
• alterations in peripheral pulses, four limb blood pressures (in some CHDs)
• dysmorphic features associated with congenital syndromes

Investigations
• CXR: cardiomegaly, pulmonary venous congestion
• ECG: sinus tachycardia, signs of underlying cause (heart block, atrial enlargement, hypertrophy, ischemia/infarct)
• Echo: structural and functional assessment
• blood work: CBC, electrolytes, BUN, Cr, LFTs
Management
• general: sitting up, O₂, sodium and water restriction, increased caloric intake
• pharmacologic: diuretics, afterload reduction (e.g. ACE inhibitor), β-blockers; digoxin rarely used
• curative: correction of underlying cause

Dysrhythmias

• see Cardiology and Cardiac Surgery, C17
• can be transient or permanent, congenital (structurally normal or abnormal), or acquired (toxin, infection, infarction)

Sinus Arrhythmia
• phasic variations with respiration (present in almost all normal children)

Sinus Tachycardia
• rate of impulses arising from sinus node is elevated (>150 bpm in infants, >100 bpm in older children)
• characterized by: beat-to-beat heart rate variability with changes in activity, P waves present/normal, PR constant, QRS narrow
• etiology: HTN, fever, anxiety, sepsis, anemia/hypoxia, PE, drugs, etc.
• differentiate from SVT (see below) by slowing the sinus rate (vagal massage, β-blockers) to identify sinus P waves

Premature Atrial Contractions
• may be normal variant or can be caused by electrolyte disturbances, hyperthyroidism, cardiac surgery, digitals toxicity

Premature Ventricular Contractions
• common in adolescents
• benign if single, uniform, disappear with exercise, and no associated structural lesions
• if not benign, may degenerate into more severe dysrhythmias

Supraventricular Tachycardia
• abnormally rapid heart rhythm originating above the ventricles – most frequent sustained dysrhythmia in children
• no beat-to-beat HR variability, >220 bpm (infants) or >180 bpm (children), P waves absent/normal, PR indeterminable, QRS usually narrow
• pre-excitation syndromes (subset of SVT): WPW syndrome, congenital defect (see Cardiology and Cardiac Surgery C23)

Complete Heart Block
• congenital heart block can be caused by maternal anti-Ro or anti-La (e.g. mother with SLE)
• often diagnosed in utero (may lead to development of fetal hydrops)
• clinical symptoms related to level of block (the lower the block, the slower the heart rate and greater the symptoms of inadequate cardiac output)
• symptomatic patients need a pacemaker

Heart Murmurs

• 50-80% of children have audible heart murmurs at some point in their childhood
• most childhood murmurs are functional (e.g. "innocent") without associated structural abnormalities and have normal ECG and radiologic findings
• in general, murmurs can become audible or accentuated in high output states (e.g. fever, anemia)

Table 11. Differentiating Heart Murmurs

<table>
<thead>
<tr>
<th></th>
<th>Innocent</th>
<th>Pathological</th>
</tr>
</thead>
<tbody>
<tr>
<td>History and Physical</td>
<td>Asymptomatic</td>
<td>Symptoms and signs of cardiac disease (FTT, exercise intolerance)</td>
</tr>
<tr>
<td>Timing</td>
<td>SEM</td>
<td>All diastolic, pansystolic, or continuous (except venous hum)</td>
</tr>
<tr>
<td>Grade/Quality</td>
<td>&lt;3/6; soft/blowing/vibratory</td>
<td>≥3/6 (palpable thrill); harsh</td>
</tr>
<tr>
<td>Splitting</td>
<td>Physiologic S2</td>
<td>May have fixed split or single S2</td>
</tr>
<tr>
<td>Extra Sounds/Clicks</td>
<td>None</td>
<td>May be present</td>
</tr>
<tr>
<td>Change of Position</td>
<td>Murmur varies</td>
<td>Unchanged</td>
</tr>
</tbody>
</table>
Table 12. Five Innocent Heart Murmurs

<table>
<thead>
<tr>
<th>Type</th>
<th>Etiology</th>
<th>Location</th>
<th>Description</th>
<th>Age</th>
<th>Differential Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peripheral</td>
<td>Pulmonic Stenosis</td>
<td>Left upper sternal border</td>
<td>Neonates, low-pitched, radiates to axilla and back</td>
<td>Neonates, usually disappears by 3-6 mo</td>
<td>PDA Pulmonary stenosis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still’s Murmur</td>
<td>Flow across the pulmonic valve leaflets</td>
<td>Left lower sternal border</td>
<td>Vibratory, LLSB or apex, SEM</td>
<td>3-6 yr</td>
<td>Subaortic stenosis Small VSD</td>
</tr>
<tr>
<td>Venous Hum</td>
<td>Altered flow in veins</td>
<td>Infraclavicular (R&gt;L)</td>
<td>Infraclavicular hum, continuous, R&gt;L</td>
<td>3-6 yr</td>
<td>PDA</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Ejection</td>
<td>Left upper sternal border</td>
<td>Soft, blowing, LUSB, SEM</td>
<td>8-14 yr</td>
<td>ASD Pulmonary stenosis</td>
</tr>
<tr>
<td>Ejection</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>Arterial Bruit</td>
<td>Supraclavicular</td>
<td>Low intensity, above clavicles</td>
<td>Any age</td>
<td>Aortic stenosis Bicuspid aortic valve</td>
</tr>
</tbody>
</table>

Infective Endocarditis

- see Infectious Diseases, ID16

Development

Approach to Global Developmental Delay

- also known as Early Developmental Impairment

Definition

- performance significantly below average in two or more domains of development (gross motor, fine motor, speech/language, cognitive, social/personal, activities of daily living) in a child <5 yr of age
- predict a diagnosis of intellectual disability in the future

Epidemiology

- 5-10% of children have neurodevelopmental delay
- careful evaluation can reveal a cause in 50-70% of cases

Etiology

- CNS abnormalities (meningitis/encephalitis, brain malformation, trauma, etc.)
- sensory deficits (hearing, vision)
- environmental (psychosocial neglect, lead exposure, antenatal drug or alcohol exposure, etc.)
- genetic/chromosomal disorders (DS, Fragile X, etc.)
- metabolic disorders (inborn errors of metabolism, hypothyroidism, iron deficiency, etc.)
- obstetrical (prematurity, HIE, TORCH infections, etc.)
- sleep disorders
- seizures

Clinical Presentation

- history
  - intrauterine exposures, perinatal events
  - detailed developmental milestones: rate of acquisition, regression of skills
  - associated problems: feeding, seizures, behaviour, sleep
  - family history, consanguinity
  - social history
- physical exam
  - dysmorphic features, hepatosplenomegaly, neurocutaneous markers, growth parameters, detailed neurological examination
- investigations (guided by history and physical examination)
  - neurodevelopmental assessment, neuroimaging, vision and hearing test, EEG, sleep study
  - OT, PT, and/or SLP assessments
  - psychosocial evaluation
  - blood work (lead, CBC, ferritin, TSH)
  - genetics consultation (microarray, Fragile X testing, testing for inborn errors of metabolism)
Management
- dependent on specific area of delay
- therapy services (e.g. speech and language therapy for language delay, OT and/or PT for motor delay), early intervention services (e.g. infant development services, Ontario Early Years Centres)

Defining Intellectual Disability
- state of functioning that begins in childhood and is characterized by limitations in both intelligence and adaptive skills
- historically defined as an IQ <70
- often preceded by diagnosis of global developmental delay

Epidemiology
- 1% of general population; M:F = 1.5:1

Etiology
- any disorder that interferes with brain development and functioning
- prenatal (majority): TORCH infections, FASD
- genetic/metabolic: DS, Fragile X, PKU, untreated or delayed diagnosis of congenital hypothyroidism, CNS abnormalities, other chromosomal/metabolic disorders

Risk Factors
- male, consanguineous parents, family history, older maternal age, decreasing maternal education, certain ethnicities
- prenatal: pre-eclampsia, maternal malnutrition or DM
- perinatal: prematurity, low birth weight, birth trauma/hypoxia
- postnatal: ICH, CNS or other serious infection, hypoxia, environmental toxins, psychosocial deprivation, malnutrition

Clinical Presentation
- history
  - well below average general intellectual functioning
  - significant deficits in adaptive functioning in at least 2 of: communication, self-care, home-living, social skills, self-direction, academic skills, work, leisure, health, safety
- physical exam
  - check growth, dysmorphic features, complete physical exam
- investigations
  - standardized psychology assessment (includes IQ test and measure of adaptive functioning)
  - vision, hearing, and neurologic assessment
  - genetic and metabolic testing as indicated

Management
- main objective: enhance adaptive functioning level
- requires an interprofessional team with strong case coordination
- emphasize community-based treatment and early intervention
- individual/family therapy, behaviour management services, therapy services (e.g. OT, SLP), medications for associated conditions
- education: life skills, vocational training, communication skills, family education
- psychosocial support for individual and family; respite care

Prognosis
- higher rates of sensory deficits, motor impairment, behavioural/emotional disorders, seizures, psychiatric illness

Language Delay

Definition
- no universally accepted definition, but often identified around 18 mo of age with enhanced well baby visit
- if formally tested, performance on a standardized assessment of language is at least one standard deviation below mean of age
- can be expressive (ability to produce or use language), receptive (ability to understand language), or both

Epidemiology
- ~10-15% of 2 yr old children have a language delay, but only 4-5% remain delayed after 3 yr of age
- ~6-8% of school-aged children have specific language impairment (many of whom were not identified before school entry)
Etiology

- cognitive disability
- constitutional language delay
- genetic/metabolic: DS, Fragile X syndrome, Williams syndrome, hypothyroidism, PKU, etc.
- hearing impairment
- mechanical problems: cleft palate, cranial nerve palsy
- medical condition: seizure disorder (includes acquired epileptic aphasia), CP, TORCH infection, iron deficiency, lead poisoning, etc.
- autism spectrum disorder
- psychosocial: neglect or abuse
- selective mutism

Risk Factors

- male, positive family history, prematurity, psychosocial (poverty, low parental education, maternal depression)

Clinical Presentation

- history
  - concerns about hearing, delay in language development or regression in previously normal language development
  - must determine if language delay is expressive, receptive, or mixed
  - children with expressive language delays may have concurrent behaviour problems or drooling (because of abnormal oral musculature)
- physical exam
  - guided by history: look for abnormal growth, dysmorphisms, unusual social interactions (lack of eye contact, not pointing)
  - include full exam of the external/internal ear (e.g. TM scarring), oral pharynx (e.g. cleft palate), and neurologic system (including tone)
- investigations
  - use of language specific screens in primary care setting: The Early Language Milestone, CAT/CLAMS, MCHAT, etc.
  - all children with suspected language delay MUST be referred to an audiologist for a hearing assessment
  - CBC (to rule out anemia), venous blood lead levels, genetic/metabolic workup as indicated

Management

- specific to etiology
- often multidisciplinary and requires appropriate referrals: early intervention services, special education services, SLP, OHNS and dental professionals, general support services
- primary care provider can help reinforce family’s understanding of delay and provide follow-up and care coordination
- prevention: parents can read aloud to their child, engage in dialogic reading, avoid baby talk, narrate daily activities, etc.

Prognosis

- depends on etiology
- if language delay persists beyond 5 yr old, more likely to have difficulties in adulthood
- persistent language delay is associated with poor academic performance, behavioural problems, social isolation

Learning Disabilities (Specific Learning Disorder DSM5)

Definition

- specific and persistent failure to acquire academic skills despite conventional instruction, adequate intelligence, and sociocultural opportunity
- a significant discrepancy between a child’s intellectual ability and their academic performance
- types: reading (dyslexia), writing, mathematics (dyscalculia)

Epidemiology

- prevalence: 10%
- high incidence of psychiatric comorbidity: anxiety, dysthymia, conduct disorder, major depressive disorder, oppositional defiant disorder, ADHD

Etiology

- pathogenesis is unknown, likely genetic factors involved
- learning disabilities may be associated with a number of conditions:
  - genetic/metabolic: Turner syndrome, Klinefelter syndrome
  - perinatal: prematurity, low birth weight, birth trauma/hypoxia
postnatal: CNS damage, hypoxia, environmental toxins, FAS, psychosocial deprivation (understimulation), malnutrition

- poor visual acuity is NOT a cause

**Risk Factors**
- positive family history, prematurity, other developmental and mental health conditions, neurologic disorders (e.g. seizure disorders, neurofibromatosis), history of CNS infection/irradiation/traumatic injury

**Clinical Presentation**
- history and physical exam
  - school difficulties (academic achievement, behaviour, attention, social interaction)
  - development of negative self-concept → reluctance to participate even in areas of strength
  - social issues: overt hostility towards parents/teachers; difficulties making friends for several reasons (problems remembering names, difficulties with language to engage in conversations, inability to understand games and complex rules, etc.), bullying, and anxiety
  - look for dysmorphisms, complete physical exam
- investigations
  - standardized tests for IQ
  - individual scores on achievement tests in reading, mathematics, or written expression (WISC III, WRAT) >2 SD below that expected for age, education, and IQ

**Management**
- provide quality instruction for specific learning disability
- support student by modifying the curriculum and/or providing accommodations (e.g. scribe for writing, extra time for tests, photocopied notes, etc.)
- consider grade retention in certain students (no guidelines exist, very rare in Ontario)
- specialized education placements that can provide educational remediation

**Prognosis**
- limited information available about persistence of learning disabilities over time
- low self-esteem, poor social skills, 40% school drop-out rate

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**Fetal Alcohol Spectrum Disorder**

**Definition**
- term describing the range of effects of prenatal exposure to alcohol, including physical, mental, behavioural, and learning disabilities
- no “safe” level of alcohol consumption during pregnancy has been established
- spectrum includes: FAS, partial FAS, ARBD, and ARND

**Epidemiology**
- prevalence of FAS and FASD is 0.1% and 1.0%, respectively
- most common preventable cause of intellectual disability

**Pathogenesis**
- specific mechanism of FASD is unknown, but hypotheses include nutritional deficits, toxic effects of acetaldehyde, alteration of placental transport, abnormal protein synthesis, and altered cerebral neurotransmission

**Diagnosis**
- often misdiagnosed or missed entirely
- diagnosis of FAS, ARBD, and ARND all require evidence of maternal drinking during pregnancy
- criteria for diagnosis of FAS
  - growth deficiency: low birth weight and/or decelerating weight over time not due to nutrition
  - characteristic pattern of facial anomalies: short palpebral fissures, flattened philtrum, thin upper lip, flat midface
  - CNS dysfunction: microcephaly and/or neurobehavioural dysfunction (hyperactivity, fine motor problems, attention deficits, learning disabilities, cognitive disabilities, difficulties in adaptive functioning, etc.)
- criteria for diagnosis of ARBD
  - congenital anomalies, including malformations and dysplasias of the cardiac, skeletal, renal, ocular, and auditory systems
- criteria for diagnosis of ARND
  - CNS dysfunction (similar to FAS)
  - complex pattern of behavioural or cognitive abnormalities inconsistent with developmental level that cannot be explained by familial background or environment alone
Management
- early diagnosis is essential to prevent secondary disabilities
- no cure, but individuals with FASD and their families should be linked to community resources and services to improve outcome

Prognosis
- secondary disabilities include unemployment, mental health problems, difficulties with the law, inappropriate sexual behaviour, disrupted school experience, peer problems

Attention Deficit Hyperactivity Disorder
- see Psychiatry, Neurodevelopmental Disorders, PS40

Autism Spectrum Disorder
- see Psychiatry, Neurodevelopmental Disorders, PS39

Motor Delay
- see Cerebral Palsy, P85 and Muscular Dystrophy, P45

Endocrinology

Antidiuretic Hormone

Diabetes Insipidus
- see Endocrinology, E19 and Nephrology, NP11

Syndrome of Inappropriate Antidiuretic Hormone
- see Endocrinology, E19 and Nephrology, NP9

Diabetes Mellitus

DIABETES MELLITUS TYPE 1
- see Disorders of Glucose Regulation, Endocrinology, E7

Epidemiology
- most common form of DM in children, M=F
- variable prevalence internationally, affects ~1:4,000 children in Canada
- can present at any age, but bimodal peaks at 5-7 yr old and at puberty

Clinical Presentation
- can present as polyuria (often manifested as nocturia or secondary enuresis), polydipsia, weight loss (lack of insulin leading to a catabolic state), polyphagia, DKA (~20%) (see Endocrinology, E11)

Management
- patients and families are best managed with a family-centered paediatric multidisciplinary team able to provide education, ongoing care, and psychosocial support surrounding survival skills, meal plans, and insulin injections as a cornerstone of treatment
- blood glucose monitoring is especially important in children as they are more susceptible to hypoglycemia
- if DKA present: ABCs, admit, monitors, correct fluid losses, administer insulin and restore glucose gradually, correct electrolyte disturbances, identify/treat precipitating event, avoid complications (i.e. cerebral edema)
- low threshold to investigate (CT/MRI) and treat DKA, as cerebral edema is a major concern
- see Endocrinology, E11
- screen for micro- and macrovascular complications (regular ophthalmology assessments, BP, microalbuminuria), concurrent autoimmune diseases (thyroiditis, celiac disease, etc.), and mental health issues (depression, eating disorders)

Diagnostic Criteria for DM (Types 1 and 2) in Children
1. Symptoms (polyuria, polydipsia, weight loss, etc…) & hyperglycemia (Random glucose ≥11.1 mmol/L)
OR,
2. Two of the following on one occasion:
   - Fasting glucose ≥7.0 mmol/L
   - 2 h plasma glucose during OGTT ≥11.1 mmol/L
   - Random glucose ≥11.1 mmol/L (not appropriate for confirmatory testing)
OR
3. One of the following on two separate occasions*
   - Fasting glucose ≥7.0 mmol/L
   - 2 h plasma glucose during OGTT ≥11.1 mmol/L
   - Random glucose ≥11.1 mmol/L (not appropriate for confirmatory testing)

* Random glucose is not appropriate for confirmatory (second) testing
Prognosis
- no cure currently
- short-term complications
  - hypoglycemia
    - due to missed/delayed meals, excess insulin or exercise, illness
    - can lead to seizures and/or coma
    - reversed with PO/IV glucose or IM glucagon
  - hyperglycemia
    - due to intercurrent illness, diet-to-insulin mismatch
    - ↑ risk of end-organ damage
  - DKA: due to missed insulin doses, infection; most common cause of death
- long-term complications
  - microvascular: retinopathy, nephropathy, neuropathy
  - macrovascular: metabolic syndrome, CVD, CAD, PVD
  - increased risk of other autoimmune diseases

DIABETES MELLITUS TYPE 2
- see Family Medicine, FM22, Endocrinology, E7
- impaired glucose metabolism due to increased peripheral insulin resistance
- rare before 10 yr of age, but more common in older children/adolescents
- prevalence is rising mainly due to the increased incidence of childhood obesity
- risk factors: obesity, positive family history, female gender, certain ethnic groups
- clinical presentation may be similar to that of type 1 DM, though most children are asymptomatic
- may present in DKA or hyperglycemic hyperosmotic nonketotic state
- management
  - initiate lifestyle modification program, including diet, weight loss, physical activity
  - glycemic target: HbA1c ≤7%
  - if glycemic targets not achieved within 3-6 mo from diagnosis with lifestyle intervention alone, either metformin, glimepiride, or insulin should be initiated
  - monitor HbA1c every 3 mo
  - advise patient to monitor finger-stick blood glucose levels if on medication with risk of hypoglycemia, are changing medication regimen, have not met treatment goals, or have intercurrent illness
- prognosis: includes microvascular and macrovascular complications similar to type 1 DM

Blood Glucose Targets by Age

<table>
<thead>
<tr>
<th>Age range</th>
<th>Pre-meal blood glucose target</th>
<th>HbA1c target</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6</td>
<td>6-10</td>
<td>&lt;6%</td>
</tr>
<tr>
<td>6-12</td>
<td>6-10</td>
<td>&lt;7.5%</td>
</tr>
<tr>
<td>&gt;12</td>
<td>4-7</td>
<td>&lt;7%</td>
</tr>
</tbody>
</table>

Management of Newly Diagnosed Type 2 DM in Children and Adolescents
Pediatrics 2013;131(2):394-42
Key Action Statements
1. Clinicians should ensure that insulin therapy is initiated for children and adolescents with type 2 DM who are ketotic or in DKA and in whom the distinction between type 1 and 2 DM is unclear and, in usual cases, should initiate insulin therapy for patients
   a. who have random venous or plasma BG concentrations 14 mmol/L, or
   b. whose HbA1c is >9%.
2. Clinicians should initiate a lifestyle modification program, including nutrition and physical activity, and start metformin as first-line therapy for children and adolescents at the time of diagnosis of type 2 DM.
3. The committee suggests that clinicians monitor HbA1c concentrations every 3 mo and intensify treatment if treatment goals for finger-stick BG and HbA1c concentrations are not being met.
4. Clinicians should advise patients to monitor finger-stick BG concentrations in patients who
   a. are taking insulin or other medications with a risk of hypoglycemia; or
   b. are initiating or changing their diabetes treatment regimen; or
   c. have not met treatment goals; or
c. have intercurrent illnesses.
5. Clinicians should incorporate the Academy of Nutrition and Dietetics’ Pediatric Weight Management Evidence-Based Nutrition Practice Guidelines in their dietary or nutrition counselling of patients with type 2 DM at the time of diagnosis and as part of ongoing management.
6. Clinicians should encourage children and adolescents with type 2 DM to engage in moderate-to-vigorous exercise for at least 60 min daily and to limit nonacademic “screen time” to less than 2 h/d.

Growth

APPROACH TO SHORT STATURE

Definition
- short stature: height <3rd percentile
- poor growth evidenced by growth deceleration (height crosses major percentile lines, growth velocity <25th percentile)

Epidemiology
- ~2.5% of the population by definition

Etiology
- see sidebar

Clinical Presentation
- history and physical exam
  - plot on growth curve (special growth charts available for Turner syndrome, achondroplasia, DS)
  - assess for dysmorphic features, disproportionate short stature
  - risk factors for GH deficiency: previous head trauma, history of intracranial bleed or infection, head surgery or irradiation, positive family history, breech delivery
  - decreased growth velocity may be more worrisome than actual height
- investigations
  - calculate mid-parental height: children are usually in a percentile between their parents’ height
  - AP x-ray of left hand and wrist for bone age
  - remaining investigations guided by history and physical (e.g. TSH, sweat chloride, etc.)

4 Questions to Ask when Evaluating Short Stature
- Was there IUGR?
- Is the growth proportionate?
- Is the growth velocity normal?
- Is bone age delayed?
Management
• depends on severity of problem as perceived by parents/child
• no treatment for non-pathological short stature, except for idiopathic short stature
• GH therapy: if administered at an early age, can help patients achieve adult height
  • requirements
    ▪ GH shown to be deficient by 2 different stimulation tests
    ▪ growth velocity <3rd percentile or height <<3rd percentile
    ▪ bone age x-rays show unfused epiphyses/delayed bone age
  • support and management of resultant self-image issues, social anxiety, etc.

Figure 7. Approach to the child with short stature

TALL STATURE
• height greater than two SD above the mean for a given age, sex, and race

Etiology
• constitutional/familial
• endocrine: Beckwith-Wiedemann syndrome, hyperthyroidism, hypophyseal gigantism, precocious puberty
• genetic: homocystinuria, Klinefelter syndrome, Marfan syndrome, Sotos syndrome

Hypercalcemia/Hypocalcemia/Rickets
• see Endocrinology, E37

Hyperthyroidism and Hypothyroidism
• may be congenital or acquired (for acquired causes, see Endocrinology, E21)

CONGENITAL HYPERTHYROIDISM
• also known as neonatal Graves’ disease

Epidemiology
• ~1:25,000 neonates, M=F

Etiology
• results from transplacental passage of maternal thyroid stimulating antibodies from mother with a history of Graves’ disease
Clinical Presentation
- history and physical exam
  - clinical manifestations may be masked if mother on antithyroid treatment
  - may present with tachycardia with CHF, heart murmur, goitre, craniosynostosis, irritability, poor feeding, FTT
- investigations:
  - serum levels of TSH and free T4 in all infants with suspected congenital hyperthyroidism or infants born to mothers with Graves’ disease

Management
- methimazole until antibodies cleared
- symptomatic treatment as needed (e.g. β-blockers to control tachycardia)

Prognosis
- if prompt and adequate treatment given, most neonates improve rapidly
- antibodies usually spontaneously cleared by 2-3 mo of life
- fetal or neonatal hyperthyroidism may have adverse effects on CNS development, leading to developmental and behaviour problems

CONGENITAL HYPOTHYROIDISM

Epidemiology
- incidence: 1:4,000-1:20,000 newborn births; F:M = 2:1
- one of the most common preventable causes of intellectual disability

Etiology
- may be classified as permanent primary, central, or transient hypothyroidism
- ~85% of primary cases are sporadic (mostly thyroid dysgenesis), remaining 15% hereditary (mostly inborn errors of thyroid synthesis)
- causes of transient hypothyroidism: maternal antibody-mediated, iodine deficiency (rare in developed countries), prenatal exposure to antithyroid medications

Clinical Presentation
- history and physical exam
  - usually asymptomatic in neonatal period because maternal T4 crosses the placenta
  - prolonged jaundice, constipation, sluggish, hoarse cry, lethargy, poor feeding, macroglossia, coarse facial features, large fontanelles, umbilical hernia
- investigations
  - diagnosis through newborn screening of TSH or free T4; abnormal results should be confirmed with serum levels from venipuncture

Management
- thyroxine replacement

Prognosis
- excellent outcome if treatment started within 1-2 mo of birth
- if treatment started after 3-6 mo of age, may result in permanent developmental delay and/or disability (mild to profound)

Sexual Development

AMBIGUOUS GENITALIA

Definition
- newborn or child whose gender is difficult to assign based on the appearance of genitalia
- subtype of DSD: a condition in which development of chromosomal, gonadal, or anatomic sex is atypical
- subtypes: 46,XX DSD, 46,XY DSD, ovotesticular DSD (true hermaphrodite)

Epidemiology
- incidence of genital abnormalities at birth is as high as 1:300
- prevalence of complex anomalies with true sexual ambiguity much lower at ~1:5,000
Etiology

- **46,XY DSD**
  - inborn error of testosterone biosynthesis or Leydig cell hypoplasia
  - 5-a-reductase deficiency, androgen receptor deficiency or insensitivity
  - LH/hCG unresponsiveness
- **46,XX DSD**
  - virilizing CAH (most common)
  - maternal source: virilizing ovarian or adrenal tumours, untreated maternal CAH, placental aromatase deficiency
- **ovotesticular DSD**
  - both ovarian follicles and seminiferous tubules in the same patient with a 46,XX karyotype
  - mixed gonadal dysgenesis

Risk Factors

- parental consanguinity, positive family history of ambiguous genitalia, early childhood illness/death, or primary amenorrhea, maternal medications during pregnancy (e.g. androgens, progesterones, danazol, phenytoin, aminoglutethimide, endocrine disruptors)

Clinical Presentation

- **history**
  - thorough obstetrical history, including prenatal screens and maternal medications
  - family history: autosomal recessive pattern may suggest CAH, X-linked recessive pattern may suggest androgen insensitivity syndrome
- **physical exam**
  - male pseudohermaphrodite (XY): small phallus, hypospadias, undescended testicles
  - female pseudohermaphrodite (XX): clitoral hypertrophy, labioscrotal fusion
  - look for concurrent midline defects, dysmorphic features, and congenital abnormalities
- **investigations**
  - karyotype and genetic workup as indicated
  - blood work: electrolytes and renin (evidence of salt-wasting in CAH); 17-OH-progesterone, androgens, FSH, and LH
  - imaging: abdominal U/S to look for uterus, testicles, ovaries

Management

- avoid announcement of probable sex or use of personal pronouns until all tests are complete
- continuous psychosocial support for parents and child during development
- elective surgical reconstruction of genitalia is sometimes possible

CONGENITAL ADRENAL HYPERPLASIA

Definition

- autosomal recessive disorder characterized by the partial or total defect of various synthetic enzymes of the adrenal cortex required for cortisol and aldosterone production

Epidemiology

- occurs in ~1:15,000 live births
- most common cause of ambiguous genitalia

Etiology

- for biosynthetic pathways of adrenal cortex, see Endocrinology, E30
- 21-OH responsible for ~95% of CAH cases
- results in ↓ cortisol and aldosterone production with shunting toward ↑ androgens
- cortisol deficiency leads to elevated ACTH, which causes adrenal hyperplasia
- rarer causes include deficiencies in 11-OH, cholesterol desmolase, 17-OH, and 3-HSD

Clinical Presentation

- depends on which enzyme in cortisol synthesis pathway is defective
- presentation of 21-OH deficiency can be divided into
  - classic deficiency with salt wasting: inadequate aldosterone resulting in FTT, hyperkalemia, hyponatremia, hypoglycemia, acidosis
  - classic deficiency without salt wasting: simple virilizing type
  - non-classic: signs/symptoms of androgen excess (e.g. amenorrhea, precocious puberty, etc.)
- 21-OH deficiency screening is part of many newborn screening programs across North America
- high serum levels of 17-OH progesterone in random blood sample diagnostic for 21-OH deficiency
Management
- correct any abnormalities in fluids, electrolytes, or serum glucose
- provide glucocorticoids/mineralocorticoids as necessary, extra glucocorticoids in times of stress
- psychosocial support

Prognosis
- complications if untreated include virilization, acne, salt wasting, hypotension

NORMAL PUBERTAL DEVELOPMENT

Physiology
- puberty occurs with the maturation of the HPG axis
- ↑ pulsatile release of GnRH → ↑ release of LH and FSH → maturation of gonads, release of sex steroids → secondary sexual characteristics
- adrenal production of androgens also required

Females
- onset: age 8-13 yr old (may start as early as 7 yr in girls of African descent)
- usual sequence
  1. thelarche: breast budding
  2. pubarche: axillary hair, body odour, mild acne
  3. growth spurt
  4. menarche: mean age 12.5 yr; indicates that growth spurt is almost complete; menses may be irregular in duration and length of cycle
- early puberty is common and often constitutional, late puberty is rare (rule out organic causes)

Males
- onset: age 9-14 yr old
- usual sequence
  1. testicular enlargement
  2. penile enlargement
  3. pubarche: axillary and facial hair, body odour, mild acne
  4. growth spurt: occurs later in boys
- early puberty is uncommon (rule out organic causes), late puberty is common and often constitutional
- gynecomastia (transient development of breast tissue) is a common self-limited condition seen in 50% of males during puberty (but any discharge from nipple or fixed mass should be investigated)

Tanner Staging
- scale used in pediatrics that defines physical measurements of development based on external primary and secondary sex characteristics

Figure 8. Tanner staging
PRECOCIOUS PUBERTY

Definition
- development of secondary sexual characteristics 2-2.5 SD before population mean
- <8 yr old for females, <9 yr old for males

Epidemiology
- 1/10,000; F>M

Etiology
- usually idiopathic in females (90%), more suggestive of pathology in males (50%)
- central (GnRH dependent)
  - hypergonadotropic hypergonadism; hormone levels as in normal puberty
  - premature activation of the HPG axis
  - differential diagnosis: idiopathic or constitutional (most common in females), CNS disturbances (tumours, hamartomas, post-meningitis, increased ICP, radiotherapy), NF, primary severe hypothyroidism
- peripheral (GnRH independent)
  - hypogonadotropic hypogonadism
  - differential diagnosis: adrenal disorders (CAH, adrenal neoplasm), testicular/ovarian tumour, gonadotropin/hCG secreting tumour (hepatoblastoma, intracranial teratoma, germinoma), exogenous steroid administration, McCune-Albright syndrome, aromatase excess syndrome, rarely hypothryoidism (Van Wyk-Grumbach syndrome)

Clinical Presentation
- history
  - symptoms of puberty, family history of precocious puberty, medical illness
- physical exam
  - growth velocity
    - prepubertal: 4 to 6 cm/yr
    - growth spurt: boys 8-10 cm/yr, girls 6-8 cm/yr
  - complete physical exam, including Tanner staging and neurological assessment
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, DHEA-S, 17-OH-progesterone)
  - secondary tests: MRI head, pelvic U/S, β-hCG, GnRH, and/or ACTH stimulation test

Management
- indications for medical intervention to delay progression of puberty: rapid advancement of puberty, early age, risk of compromise of final adult height, psychological
- central causes: goals are to preserve height and alleviate psychosocial stress; GnRH agonists (e.g. leuprolide) most effective
- peripheral causes: goal is to limit effects of elevated sex steroids; treat underlying cause; medications that decrease the production of a specific sex steroid or block its effects (e.g. ketoconazole, spironolactone, tamoxifen, anastrozole), surgical intervention

DELAYED PUBERTY

Definition
- failure to develop secondary sex characteristics by 2-2.5 SD beyond the population mean
- for males: lack of testicular enlargement by 14 yr old
- for females: lack of breast development by 13 yr old OR absence of menarche by 16 yr old or within 5 yr of pubertal onset

Epidemiology
- M>F

Etiology
- usually constitutional delay in males, more suggestive of pathology in females
- central causes
  - constitutional delay in activation of HPG axis (most common)
  - hypogonadotropic hypogonadism
- peripheral causes
  - hypergonadotropic hypogonadism (e.g. primary gonadal failure, gonadal damage, Turner syndrome, hormone deficiency, androgen insensitivity syndrome, etc.)
Clinical Presentation

- history: weight loss, short stature, family history of puberty onset, medical illness, high performance athletes (females)
- physical exam: growth velocity (minimum 4 cm/yr), Tanner staging, neurological exam, complete physical exam
- investigations
  - initial screening tests: bone age, serum hormone levels (estradiol, testosterone, LH, FSH, TSH, free T4, IGf-1), CBC, electrolytes, BUN, Cr, LFTs, liver enzymes, ESR, CRP, urinalysis
  - secondary tests: MRI head, pelvic U/S, karyotype, IBD panel, celiac disease panel, LH levels following GnRH agonist

Management

- identify and treat underlying cause
- hormonal replacement: cyclic estradiol and progesterone for females, testosterone for males

Gastroenterology

Vomiting

History

- characteristic of emesis (e.g. projectile, bilious, bloody)
- pattern of emesis (e.g. association with feeds, cyclic, morning)
- associated symptoms (e.g. anorexia, diarrhea, etc.)
- red flags: bilious or bloody emesis, projectile vomit, abdominal distension and tenderness, high fever, signs of dehydration
- note that vomiting without diarrhea is most likely not gastroenteritis

Physical Findings

- vital signs to determine clinical status and hydration state

Investigations

- CBC, electrolytes, BUN, Cr, amylase, lipase, glucose done routinely
- in sick child, add: ESR, venous blood gases, C&S (blood, stool), imaging

<table>
<thead>
<tr>
<th>Table 13. Common Differential Diagnosis, Associated Findings, and Diagnostic Approach Based on Age</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cause</strong></td>
</tr>
<tr>
<td>NEONATES – NON-BILIOUS</td>
</tr>
<tr>
<td>Tracheoesophageal Fistula</td>
</tr>
<tr>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td>GERD</td>
</tr>
<tr>
<td>Sepsis</td>
</tr>
<tr>
<td>Inborn error of metabolism</td>
</tr>
<tr>
<td>NEONATES – BILIOUS</td>
</tr>
<tr>
<td>Malrotation with volvulus</td>
</tr>
<tr>
<td>Duodenal atresia</td>
</tr>
<tr>
<td>Hirschsprung’s disease</td>
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</tbody>
</table>
### Table 13. Common Differential Diagnosis, Associated Findings, and Diagnostic Approach Based on Age (continued)

<table>
<thead>
<tr>
<th>Cause</th>
<th>Suggestive Findings</th>
<th>Diagnostic Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CHILDREN AND ADOLESCENTS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>Diarrhea, fever, sick contact, recent travel</td>
<td>CBC, stool culture</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Periumbilical discomfort that later localizes to RLQ, fever, anorexia</td>
<td>Abdominal U/S</td>
</tr>
<tr>
<td>Intussusception</td>
<td>Colicky progressive abdominal pain, drawing of legs up to chest, lethargy, bloody “red currant jelly” stool</td>
<td>Abdominal U/S</td>
</tr>
<tr>
<td>Non-GI infection (e.g. meningitis)</td>
<td>Fever, localized findings depending on cause</td>
<td>Cultures (CSF, blood, urine), brain imaging, CXR</td>
</tr>
<tr>
<td>Increased ICP</td>
<td>Nocturnal waking, progressive recurrent headache worse with Valsalva, nuchal rigidity</td>
<td>Brain CT without contrast</td>
</tr>
<tr>
<td>Toxic ingestion</td>
<td>Finding possibly varying by substance-toxidrome, often a history of ingestion</td>
<td>Qualitative and sometimes quantitative levels (urine, blood)</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Amenorrhea, morning sickness, bloating, breast tenderness</td>
<td>Urine ß-hCG</td>
</tr>
<tr>
<td>Cyclic vomiting</td>
<td>At least 3 self-limited episodes of vomiting lasting 12 h, 7 d between episodes, no organic cause of vomiting</td>
<td>Diagnosis of exclusion</td>
</tr>
</tbody>
</table>

**Management**
- rehydration (see Fluids and Electrolytes, P76)
- treat underlying cause

### Gastroesophageal Reflux

**Epidemiology**
- extremely common in infancy (up to 50%)

**Clinical Presentation**
- vomiting typically soon after feeding, non-bilious, rarely contains blood, small volume (<30 mL)

**Investigations**
- thriving baby requires no investigation
- investigations required if concomitant FTT, feeding aversion, recurrent cough, pneumonia or bronchospasm, GI blood loss or symptoms persist after 18 mo

**Management**
- conservative: thickened feeds, frequent and smaller feeds, elevation of head
- medical
  - short-term parenteral feeding to enhance weight gain
  - ranitidine, PPI: decreases gastric acidity, decreases esophageal irritation
  - domperidone, metoclopramide: improves gastric emptying and GI motility; safety concerns and limited efficacy, should be reserved for children with gastroparesis contributing to GERD
- surgical: indicated for failure of medical therapy (Nissen fundoplication)

**Complications**
- esophagitis, strictures, Barrett’s esophagus, FTT, aspiration, oral feeding aversion
Tracheoesophageal Fistula
• see General Surgery, GS66

Pyloric Stenosis
• see General Surgery, GS63

Duodenal Atresia
• see General Surgery, GS65

Malrotation of the Intestine
• see General Surgery, GS64

Diarrhea
• definition of diarrhea varies with diet and age (stool normalcy difficult to define in children)
  • infants → increase in stool frequency to twice as often per day; older children → 3+ loose or watery stools/d
  • duration: acute: <2 wk; chronic: >2 wk

Pathophysiology
• osmotic: due to non-absorbable solutes in GI tract (e.g. lactose intolerance)
• secretory: increased secretion of Cl⁻ ions and water in intestinal lumen (e.g. bacterial toxin)
• malabsorption: decreased GI surface area (e.g. short bowel syndrome)

History
• frequency, duration, quality of diarrhea
• associated symptoms (e.g. fever, abdominal pain, hematochezia, etc.)
• recent antibiotic use or recent travel
• elements of diet

Physical Findings
• vital signs to determine clinical status and hydration state

Investigations
• acute diarrhea
  • stool for C&S, O&P, electron microscopy for viruses, C. difficile toxin, microscopy (leukocytes suggestive of invading pathogen), blood and urine cultures, blood work
  • chronic diarrhea
  • serial heights, weights, growth percentiles
  • if child growing well and thriving, workup is limited (stool cultures as above, stool reducing substances)
  • red flags: poor growth, chronic rash, other serious infections, hospitalizations for dehydration
    • require full workup (as per below)
  • stool: consistency, pH, reducing substances, microscopy, occult blood, O&P, C&S, C. difficile toxin, 3 d fecal fat, α-1-antitrypsin clearance, fecal elastase
  • urinalysis, urine culture
  • CBC, differential, ESR/CRP, smear, electrolytes, total protein, albumin, carotene, Ca²⁺, PO₄³⁻, Mg²⁺, Fe, ferritin, folate, fat-soluble vitamins, PTT, INR
  • sweat chloride, celiac screen, thyroid function tests, urine VMA and HVA, HIV test, lead levels
  • CXR, upper GI series and follow-through
  • specialized tests: endoscopy, small bowel biopsy

Diarrhea is defined as an increase in frequency and/or decreased consistency of stools compared to normal
Normal stool volume
Infants: 5-10 g/kg/d
Children: 200 g/d

Diarrhea Red Flags
Bloody stool, fever, petechiae or purpura, signs of severe dehydration, weight loss/FTT

Common Antibiotics that Can Lead to C. difficile Infection
• Fluoroquinolones
• Clindamycin
• Penicillin (broad spectrum)
• Cephalosporins (broad spectrum)
Differential Diagnosis

Table 14. Differential Diagnosis of Diarrhea

<table>
<thead>
<tr>
<th>Infections</th>
<th>Acute</th>
<th>Chronic 0 – 3 mo</th>
<th>3 mo – 3 yr</th>
<th>3 – 18 yr</th>
<th>Uncommon</th>
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<tbody>
<tr>
<td>Infectious</td>
<td>Viral</td>
<td>Gi infection</td>
<td>Gi infection</td>
<td>Gi infection</td>
<td>Drug-induced</td>
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<td></td>
<td>Rotavirus</td>
<td>Toddler’s diarrhea</td>
<td>Lactase deficiency</td>
<td>Lactase deficiency</td>
<td>Chronic constipation</td>
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<td></td>
<td>Norwalk</td>
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<td>UTI</td>
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<td>Enteric adenovirus</td>
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<td>Bacterial</td>
<td>Salmonella</td>
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<td></td>
<td>Campylobacter</td>
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<td></td>
<td>Shigella</td>
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<tr>
<td></td>
<td>Pathogenic E. coli</td>
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<tr>
<td></td>
<td>Yersinia</td>
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<tr>
<td></td>
<td>C. difficile</td>
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<tr>
<td>Parasitic</td>
<td>Giardia lamblia</td>
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<td>Entamoeba histolytica</td>
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<td>Non-infectious</td>
<td>Antibiotic-induced</td>
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<td>Non-specific: associated with systemic infection</td>
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<td></td>
<td>Non-specific: associated with Hirschsprung’s disease</td>
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<td></td>
<td>Toxic ingestion</td>
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<tr>
<td></td>
<td>Primary disaccharidase deficiency</td>
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Chronic

<table>
<thead>
<tr>
<th>FTT</th>
<th>No FTT</th>
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<tr>
<td>0 – 3 mo</td>
<td>3 –18 yr</td>
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<tr>
<td>GI infection</td>
<td>GI infection</td>
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<tr>
<td>Toddler’s diarrhea</td>
<td>Lactase deficiency</td>
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<tr>
<td>IBD</td>
<td>Irritable bowel syndrome</td>
</tr>
<tr>
<td>Endocrine (thyrotoxicosis, Addison’s)</td>
<td>Neoplastic (pheochromocytoma, lymphoma)</td>
</tr>
<tr>
<td>Short bowel syndrome</td>
<td>Schwachman-Diamond syndrome</td>
</tr>
</tbody>
</table>

Gastroenteritis

History
- non-specific: diarrhea, vomiting, fever, anorexia, headache, myalgias, abdominal cramps
- bacterial and parasitic agents more common in older children (2-4 yr)
- recent infectious contacts: symptoms usually begin 24-48 h after exposure

Physical Exam
- febrile
- dehydrated: must assess extent (see Dehydration, P76)

Investigations
- not usually necessary in young children
- stool analysis: leukocytes/erythrocytes suggests bacterial or parasitic etiology; pH <6 and presence of reducing substances suggests viral etiology

Complications
- viral gastroenteritis usually self-limiting (lasts 3-7 d in most cases)
- adverse effects related to hypovolemia, shock, tissue acidosis, and rapid onset and over-correction of electrolyte imbalances
- death in severe dehydration (rare in developed countries)

Table 15. Gastroenteritis

<table>
<thead>
<tr>
<th>Viral Infection</th>
<th>Bacterial Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Most common cause of gastroenteritis Commonly: rotaviruses (most common), enteric adenovirus, norovirus (typically older children)</td>
</tr>
<tr>
<td></td>
<td>Salmonella, Campylobacter, Shigella, pathogenic E. coli, Yersinia, C. difficile</td>
</tr>
<tr>
<td>Clinical Presentation</td>
<td>Associated with URTIs Resolves in 3-7 d Slight fever, malaise, vomiting, vague abdominal pain</td>
</tr>
<tr>
<td></td>
<td>Severe abdominal pain High fever Bloody diarrhea</td>
</tr>
<tr>
<td>Risk Factors</td>
<td>Day care, young age, sick contacts, immunocompromised Bacterial infection: travel, poorly cooked meat, poorly refrigerated foods, antibiotics</td>
</tr>
<tr>
<td>Management</td>
<td>Prevention and treatment of dehydration most important (see Dehydration, P76) Early refeeding advisable, with age-appropriate diet upon completion of rehydration Ondansetron for suspected gastroenteritis with mild to moderate dehydration or failed ORT and significant vomiting Antibiotic or antiparasitic therapy when indicated, antidiarrheal medications not indicated Notify Public Health authorities if appropriate Promote regular hand-washing and return to school 24 h after last diarrheal episode to prevent transmission Rotavirus vaccine</td>
</tr>
</tbody>
</table>
**Toddler’s Diarrhea**

**Epidemiology**
- most common cause of chronic diarrhea during infancy
- onset between 6-36 mo of age, ceases spontaneously between 2-4 yr

**Clinical Presentation**
- diagnosis of exclusion in thriving child
- 4-6 bowel movements per day
- diet history (e.g. excess juice intake overwhelms small bowel resulting in disaccharide malabsorption)
- stool may contain undigested food particles
- excoriated diaper rash

**Management**
- reassurance that it is self-limiting
- 4Fs (adequate fibre, normal fluid intake, 35-40% fat, discourage excess fruit juice)

**Lactase Deficiency (Lactose Intolerance)**

**Clinical Presentation**
- chronic, watery diarrhea and abdominal pain, bloating associated with dairy intake
- primary lactose intolerance: crampy abdominal pain with loose stool (older children, usually of East Asian and African descent)
- secondary lactose intolerance: older infant, persistent diarrhea (post viral/bacterial infection, celiac disease, or IBD)

**Diagnosis**
- trial of lactose-free diet
- watery stool, acid pH, positive reducing sugars
- positive breath hydrogen test if >6 yr

**Management**
- lactose-free diet, soy formula
- lactase-containing tablets/capsules/drops (e.g. Lacteeze®, Lactaid®)

**Irritable Bowel Syndrome**
- see Gastroenterology, G23

**Celiac Disease**
- see Gastroenterology, G18
- in children: presents at any age, usually 6-24 mo with the introduction of gluten in the diet
- FTT with poor appetite, irritability, apathy, rickets, wasted muscles, flat buttocks, rarely distended abdomen
- GI symptoms: anorexia, N/V, edema, anemia, abdominal pain
- non-GI manifestations: iron-deficiency anemia, dermatitis herpetiformis, dental enamel hypoplasia, osteopenia/osteoporosis, short stature, delayed puberty, behavioural changes
- associated with other autoimmune disorders

**Milk Protein Allergy**

**Pathophysiology**
- immune-mediated mucosal injury (IgE- and non-IgE-mediated)

**Clinical Presentation**
- up to 50% of children intolerant to cow’s milk may be intolerant to soy protein as well
- often history of atopy
- can present as
  - proctocolitis: mild diarrhea, small amounts of bloody stools (common presentation in young infant)
  - enterocolitis: vomiting, diarrhea, anemia, hematochezia
  - enteropathy: chronic diarrhea, hypoalbuminemia

A Celiac disease diet must avoid gluten present in “BROW” foods
Barley
Rye
Oats (controversial)
Wheat

Celiac disease is associated with an increased prevalence of IgA deficiency. Since tTG is an IgA-detecting test, you must order an accompanying IgA level.
Management
• casein hydrolysate formula (dairy-free e.g. Nutramigen®, Pregestimil®) or mother may remove all milk protein from diet and continue breastfeeding (with adequate calcium and vit D intake)
• often outgrow by 1 yr of age

Inflammatory Bowel Disease
• see Gastroenterology, G19

Cystic Fibrosis
• see Respirology, P90

Constipation
• decreased stool frequency (<3 stools/wk) and/or stool fluidity (hard, pellet-like)

FUNCTIONAL CONSTIPATION
• 99% of cases of constipation
• Rome III criteria; ≥2 of the following
  ▪ ≤2 defecations in the toilet/wk
  ▪ ≥1 episode of fecal incontinence/wk
  ▪ history of retentive posturing or excessive volitional stool retention
  ▪ history of painful or hard bowel movements
  ▪ large fecal mass in rectum
  ▪ history of large diameter stools that may obstruct toilet

Pathophysiology
• lack of fibre in diet or change in diet, poor fluid intake, behavioural
  ▪ infants: often occurs when introducing cow’s milk after breast milk due to high fat and solute content, lower water content
  ▪ toddlers/older children: can occur during toilet training, or due to pain on defecation, leading to withholding of stool
  ▪ two crucial time periods: toilet training and starting school

Management
• education: explanation of mechanism of functional constipation for parents/older children
• clean out: PEG 3350 flakes (1-1.5 g/kg/d, max 100 g/d), picosalax, PEGlyte®
• maintenance: adequate fluid intake (if <6 mo, 150 mL/kg/d), adequate dietary fibre (fruit, vegetables, whole grains), stool softening (PEG 3350, mineral oil), appropriate toilet training technique (dedicated time for defecation: 3-10 min, 1-2 x/d)
• children should be treated for at least 6 mo, and should not be weaned from maintenance therapy until they are having regular bowel movements without difficulty
• regular follow-up with ongoing support and encouragement is essential

Complications
• pain retention cycle: anal fissures + pain → withhold passing stool → chronic dilatation ± overflow incontinence

HIRSCHSPRUNG’S DISEASE (Congenital Aganglionic Megacolon)
• see General Surgery, GS65

OTHER ORGANIC DISORDERS CAUSING CONSTIPATION
• endocrine: hypothyroidism, DM, hypercalcemia
• neurologic: spinal cord abnormalities/trauma, NF
• anatomic: bowel obstruction, anus (imperforate, atresia, stenosis, anteriorly displaced)
• drugs: lead, chemotherapy, opioids
• others
Abdominal Pain

ACUTE ABDOMINAL PAIN

History
• description of pain (location, radiation, duration, constant vs. colicky, relation to meals)
• associated symptoms: N/V, diarrhea, fever

Physical Exam
• abdominal exam, rectal exam, rash

Investigations
• CBC, differential, urinalysis to rule out UTI

Table 16. Differential Diagnosis of Acute Abdominal Pain

<table>
<thead>
<tr>
<th>Gastrointestinal</th>
<th>Hepatobiliary Tract</th>
<th>Genitourinary</th>
<th>Hematologic</th>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastroenteritis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendicitis</td>
<td>Cholecystitis</td>
<td>UTI</td>
<td>Henoch-Schönlein purpura</td>
<td></td>
</tr>
<tr>
<td>Meckel’s diverticulum</td>
<td>Pancreatitis</td>
<td>Testicular torsion</td>
<td>Sickle cell crisis</td>
<td>DKA</td>
</tr>
<tr>
<td>Mesenteric adenitis</td>
<td></td>
<td>Ovarian torsion</td>
<td></td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Ileus</td>
<td></td>
<td>Intestinal obstruction</td>
<td></td>
<td>Somatization</td>
</tr>
<tr>
<td>Intestinal obstruction</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(incarcerated hernia, intussusception, volvulus)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malabsorption</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IBS</td>
<td>Constipation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>APPENDICITIS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
• see General Surgery, GS28
• most common cause of acute abdomen after 5 yr of age
• clinical features: low grade fever, abdominal pain, anorexia, N/V (after onset of pain), peritoneal signs (generalized peritonitis is a common presentation in infants/young children)
• treatment: surgical
• complications: perforation (common in young children), abscess

INTUSSUSCEPTION
• telescoping of segment of bowel into distal segment causing ischemia and necrosis

Epidemiology
• 90% idiopathic, children with CF or GJ tube at significantly increased risk; M:F = 3:1
• 50% between 3-12 mo, 75% before 2 yr of age

Pathophysiology
• usual site: ileocecal junction; jejunum in children with GJ tubes
• lead point of telescoping segment may be swollen Peyer’s patches, Meckel’s diverticulum, polyp, malignancy, HSP, structural abnormalities

Clinical Presentation
• “classic triad” (<25% patients) - abdominal pain, palpable mass, red currant jelly stools
• often preceded by URTI
• sudden onset of recurrent, paroxysmal, severe periumbilical pain with pain-free intervals
• later vomiting (may be bilious) and rectal bleeding (late finding)
• shock and dehydration; lethargy may be only presenting symptom

Diagnosis
• U/S, air enema

Management
• air enema can be therapeutic (reduces intussusception in 75% of cases), reduction under hydrostatic pressure, surgery rarely needed
• recurrence rate 10-15%, need to consider pathologic lead point
### Chronic Abdominal Pain

#### Epidemiology
- prevalence: 10% of school children (peak at 8-10 yr), F>M

#### Etiology
- organic (<10%)
  - gastrointestinal
    - constipation (cause vs. effect), infectious
    - IBD, esophagitis, peptic ulcer disease, lactose intolerance
  - anatomic anomalies, masses
  - pancreatic, hepatobiliary
  - genitourinary causes: recurrent UTI, nephrolithiasis, chronic PID, Mittelschmerz
  - neoplastic
- functional abdominal pain (90%): can be diagnosed when there are no alarm symptoms or signs, physical exam is normal, and stool sample tests are negative for occult blood; no further testing is required, unless high suspicion for organic cause

#### Clinical Presentation
- clustering episodes of vague, crampy periumbilical/epigastric pain, vivid pain description
- seldom awakens child from sleep, less common on weekends
- aggravated by exercise, alleviated by rest
- psychological factors related to onset and/or maintenance of pain, school avoidance
- psychiatric comorbidity: anxiety, somatoform, mood, learning disorders, sexual abuse, eating disorders, elimination disorders
- diagnosis of exclusion

#### Investigations
- fecal occult blood and others based on clinical suspicion (CBC, ESR, urinalysis, etc.)

#### Management
- continue to attend school
- manage any emotional or family problems, counselling, CBT
- trial of high fibre diet, trial of lactose-free diet
- possible role for amitriptyline
- reassurance

#### Prognosis
- pain resolves in 30-50% of children within 2-6 wk of diagnosis
- 30-50% of children with functional abdominal pain have functional pain as adults (e.g. IBS)

### Abdominal Mass

#### Table 17. Differential Diagnosis for Abdominal Mass

<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal (note: 50% of abdominal masses in newborn are renal in origin)</td>
<td>Hydro nephrosis</td>
</tr>
<tr>
<td></td>
<td>Polycystic kidney disease</td>
</tr>
<tr>
<td></td>
<td>Hamartoma</td>
</tr>
<tr>
<td>Adrenal</td>
<td>Ovarian cysts</td>
</tr>
<tr>
<td>Ovarian</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>Hepatomegaly/splenomegaly</td>
</tr>
<tr>
<td></td>
<td>Pyloric stenosis</td>
</tr>
<tr>
<td></td>
<td>Abdominal hernia</td>
</tr>
<tr>
<td></td>
<td>Teratoma</td>
</tr>
<tr>
<td></td>
<td>Fecal impaction</td>
</tr>
</tbody>
</table>

### Upper Gastrointestinal Bleeding
- see Gastroenterology, G25
Lower Gastrointestinal Bleeding

• see Gastroenterology, G27

Etiology
• acute
  ▪ infectious (bacterial, parasitic)
  ▪ antibiotic-induced (C. difficile)
  ▪ NEC in preterm infants
  ▪ anatomic
  ▪ malrotation/volvulus, intussusception
  ▪ Meckel's diverticulitis
  ▪ anal fissures, hemorrhoids
  ▪ vascular/hematologic
  ▪ HSP
  ▪ HUS
  ▪ coagulopathy

• chronic
  ▪ anal fissures (most common)
  ▪ colitis
  ▪ IBD
  ▪ allergic (milk protein)
  ▪ structural
  ▪ polyps (most are hamartomas)
  ▪ neoplasms (rare)
  ▪ coagulopathy

Physical Exam
• hemodynamic status, evidence of FTT, fever
• anal and rectal exam: tags, fissures, anal fistulas, polyps, foreign body, blood per rectum
• stool appearance
• NG aspirate
• lower GI bleed may present as melena (if it involves the small bowel) or hematochezia

Investigations
• stool cultures (C&S, C. difficile toxin)
• urinalysis and microscopy
• CBC, smear, differential, ESR, CRP, electrolytes, urea, Cr, INR, PTT, albumin, iron studies, amoeba titers
• radiologic investigations (including abdominal x-ray to rule out obstruction)
• Meckel's radionuclide scan

Management
• acute stabilization: ABCs, volume and blood replacement, bowel rest (NPO, NG tube)
• once stable, endoscopy and/or surgery as indicated

Genetics, Dysmorphisms, and Metabolism

Genetics

MECHANISMS OF INHERITANCE

Mendelian Inheritance
• disorders caused by mutation of one or both copies of a gene, inherited in one of two patterns
  ▪ autosomal: encoded by genes on one of 22 pairs of autosomes (chromosomes 1-22)
  ▪ X-linked: encoded by a gene on the X chromosome

Triplet Repeat Expansions
• disorder in which trinucleotide repeats in certain genes exceed the normal number and result in altered expression of the gene or production of an abnormal protein (e.g. Fragile X syndrome, spinocerebellar ataxias, myotonic dystrophy, Huntington disease)

Imprinting Disorders
• imprinting: epigenetic process that involves methylation or acetylation of DNA, affecting gene expression
• imprinted genes are expressed differently depending on whether they are inherited from the mother or the father (parent-of-origin gene expression)
• occur when imprinted alleles are silenced (e.g. Prader-Willi syndrome, Angelman syndrome, Beckwith-Wiedemann syndrome)

Mitochondrial Inheritance
• disorders caused by mutations of the DNA present in mitochondria
• inheritance pattern: mother passes on the defect to all her children; father does not pass on the defect since embryo only receives mitochondria from the mother (in the egg)
METHODS OF GENETIC TESTING

- microarray analysis
  - a microarray is a collection of DNA probes attached to a solid surface
  - microarray analysis can identify small deletions or duplications of genetic material anywhere in the genome
  - indicated when there is developmental delay + one or more major malformations
- FISH: usually to identify a gain or loss of chromosomal material
- karyotype: microscopic analysis of all 46 chromosomes with a special stain that shows large changes in the number or structure of chromosomes

Genetic Anomalies

Minor and Major Anomalies

- minor anomaly: an unusual anatomic feature that is of no serious medical or cosmetic consequence to the patient
- major anomaly: anomaly that creates significant medical, surgical, or cosmetic problems for the patient

Mechanism for Anomalies

- malformation: results from an intrinsically abnormal developmental process (e.g. polydactyly)
- disruption: results from the extrinsic breakdown of, or interference with, an originally normal developmental process (e.g. amniotic band disruption sequence)
- deformation: alteration of the final form of a structure by mechanical forces (e.g. Potter deformation sequence)
- dysplasia: abnormal development that results in abnormal organization of cells into tissues (e.g. bone dysplasia)

Multiple Anomalies

- association: non-random occurrence of multiple independent anomalies that appear together more than would be predicted by chance but are not believed to have a single etiology (e.g. VACTERL)
- sequence: related anomalies that come from a single initial major anomaly or precipitating factor that changes the development of other surrounding or related tissues or structures (e.g. Potter sequence)
- syndrome: a pattern of anomalies that occur together and are caused by a single known or unknown cause (e.g. Down syndrome)

Approach to the Dysmorphic Child

- genetic disorders are the most common cause of infant death in developed countries

General Approach to the Dysmorphic Child

- Are the anomalies major or minor?
- What is the mechanism underlying the anomaly?
- Do the anomalies fit as part of an association, sequence, or syndrome?

History

- prenatal/obstetrical history (see Obstetrics, OB4) with particular attention to potential teratogenic exposures
- complete 3 generation family pedigree: consanguinity, stillbirths, neonatal deaths, specific illnesses, intellectual disability, multiple miscarriages, ethnicity
**Physical Exam**

**Investigations**
- screening for TORCH infections
- serial photographs if child is older
- x-rays for bony abnormalities
- cytogenetic studies
  - karyotype if recognized syndrome
  - chromosome microarray analysis (array comparative genomic hybridization) if developmental delay with one or more congenital anomalies
  - FISH if microdeletion syndrome or trisomy suspected
- biochemistry: specific enzyme assays
- single gene testing

**Management**
- prenatal counselling and assessing risk of recurrence
- referral for specialized pediatric or genetic care

**Genetic Syndromes**

**Table 18. Common Genetic Syndromes**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>1:600-800 births</td>
<td>Most common abnormality of autosomal chromosomes</td>
<td>1:10,000 live births</td>
</tr>
<tr>
<td>Cranium/Brain</td>
<td>Mild microcephaly, flat occiput, 3rd fontanelle, brachycephaly</td>
<td>Microcephaly, prominent occiput</td>
<td>Microcephaly, sloping forehead, occipital scalp defect, holoprosencephaly</td>
</tr>
<tr>
<td>Eyes</td>
<td>Upslanting palpebral fissures, inner epicanthal folds, speckled iris (Brushfield spots), refractive errors (myopia), acquired cataracts, nystagmus, strabismus</td>
<td>Microphthalmia, hypotelorism, iris coloboma, retinal anomalies</td>
<td>Microphthalmia, corneal abnormalities</td>
</tr>
<tr>
<td>Ears</td>
<td>Low-set, small, overlapped upper helix, frequent AOM, hearing loss</td>
<td>Low-set, malformed</td>
<td>Low-set, malformed</td>
</tr>
<tr>
<td>Facial Features</td>
<td>Protruding tongue, large cheeks, low flat nasal bridge, small nose</td>
<td>Cleft lip/palate</td>
<td>Cleft lip/palate, 60-80% cleft lip and palate</td>
</tr>
<tr>
<td>Skeletal/MSK</td>
<td>Short stature</td>
<td>Short stature</td>
<td>Severe growth retardation</td>
</tr>
<tr>
<td>Cardiac Defect</td>
<td>50%, particularly atrioventricular septal defect</td>
<td>60% (VSD, PDA, ASD)</td>
<td>80% (VSD, PDA, ASD)</td>
</tr>
<tr>
<td>GI</td>
<td>Duodenal/esophageal/anal atresia, TEF, Hirschsprung’s disease, chronic constipation</td>
<td>Hemia, TEF</td>
<td>Polycystic kidneys, cryptorchidism</td>
</tr>
<tr>
<td>GU</td>
<td>Cryptorchidism, rarely fertile</td>
<td>Polycystic kidneys</td>
<td>Polycystic kidneys</td>
</tr>
</tbody>
</table>
Table 18. Common Genetic Syndromes (continued)

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Trisomy 21</th>
<th>Trisomy 18</th>
<th>Trisomy 13</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Hypotonia at birth Low IQ, developmental delay, hearing problems Onset of Alzheimer’s disease in 40s</td>
<td>Hypertonia</td>
<td>Hypo- or hypertonia Seizures, deafness Severe developmental delay</td>
</tr>
<tr>
<td>Other Features</td>
<td>Transverse palmar crease, clinodactyly, and absent middle phalanx of the 5th finger 1% lifetime risk of leukemia Polycythemia Hypothyroidism</td>
<td>SGA Rocker-bottom feet</td>
<td>Single umbilical artery Midline anomalies: scalp, pituitary, palate, heart, umbilicus, anus Rocker-bottom feet</td>
</tr>
<tr>
<td>Prognosis/Management</td>
<td>Prognosis: long-term management per AAP Guidelines (Health Supervision of Children with Down syndrome), recommend chromosomal analysis, CBC, Echo, yearly thyroid test, atlanto-occipital x-ray at 2 yr; sleep study, hearing test, and ophthalmology assessment</td>
<td>44% die in 1st month 10% survive past 1 yr Profound intellectual disability in survivors</td>
<td>33% die in 1st month, 50% by 2nd month, 90% by 1 yr from FTT Profound intellectual disability in survivors</td>
</tr>
</tbody>
</table>

Table 19. Most Common Sex Chromosome Disorders

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Fragile X Syndrome</th>
<th>Klinefelter Syndrome</th>
<th>Turner Syndrome</th>
<th>Noonan Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>X-linked</td>
<td>Genetic anticipation</td>
<td>47,XXY (most common)</td>
<td>46,XX or 46,XY</td>
</tr>
<tr>
<td></td>
<td>CGG trinucleotide repeat on X chromosome measurable by molecular analysis</td>
<td>48,XXXY, 49,XXXXY</td>
<td>Autosomal dominant (not a sex chromosome disorder) with variable expression</td>
<td></td>
</tr>
<tr>
<td>Incidence</td>
<td>1:3,600 males, 1:6,000 females</td>
<td>Most common heritable cause of intellectual disability in boys</td>
<td>1:4,000 live female births</td>
<td>1:2,000 male and female live births</td>
</tr>
<tr>
<td>Phenotype</td>
<td>Overgrowth: prominent jaw, forehead, and nasal bridge with long and thin face, large protuberant ears, macroorchidism, hypertensibility, and high arched palate Complications: seizures, scoliosis, mitral valve prolapse</td>
<td>Tall, slim, underweight</td>
<td>Short stature, short webbed neck, low posterior hair line, wide carrying angle Broad chest, widely spaced nipples Lymphedema of hands and/or feet, cystic hygroma in newborn with polyhydramnios, lung hypoplasia Coarctation of aorta, bicuspid aortic valve</td>
<td>Certain phenotypic features similar to females with Turner syndrome; therefore, sometimes called the “male Turner syndrome”, although it affects both males and females</td>
</tr>
<tr>
<td>IQ and Behaviour</td>
<td>Mild to moderate intellectual disability, 20% of affected males have normal IQ ADHD and/or autism Female carriers may show intellectual impairment Male carriers may demonstrate tremor/ataxia syndrome in later life</td>
<td>Mild intellectual disability Behavioural or psychiatric disorders – anxiety, shyness, aggressive behaviour, antisocial acts</td>
<td>Mild intellectual disability to normal intelligence Moderate intellectual disability in 25% of patients</td>
<td></td>
</tr>
<tr>
<td>Gonad and Reproductive Function</td>
<td>Premutation carrier females at risk of developing premature ovarian failure</td>
<td>Infertility due to hypogonadism/ hypospermatia</td>
<td>Streak ovaries with deficient follicles, infertility, primary amenorrhea, impaired development of secondary sexual characteristics</td>
<td>Delayed puberty</td>
</tr>
<tr>
<td>Diagnosis/Prognosis/Management</td>
<td>Molecular testing of FMR1 gene: overamplification of the trinucleotide repeat, length of segment is proportional to severity of clinical phenotype (genetic anticipation)</td>
<td>Increased risk of germ cell tumours and breast cancer Management: testosterone in adolescence</td>
<td>Normal life expectancy if no complications Increased risk of X-linked diseases Management: Echo, ECG to screen for cardiac malformation GH therapy for short stature Estrogen replacement at time of puberty for development of secondary sexual characteristics</td>
<td>Molecular testing of PTPN11 gene Management: affected males may require testosterone replacement therapy at puberty Echo, ECG</td>
</tr>
</tbody>
</table>
Table 20. Other Genetic Syndromes

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Genotype</th>
<th>Incidence</th>
<th>Clinical Features</th>
</tr>
</thead>
</table>
| **DiGeorge Syndrome** | Microdeletions of chromosome region 22q11    | 1:15,000             | "CATCH 22"  
Cyanotic CHD  
Anomalies: craniofacial anomalies typically micrognathia and low set ears  
Thymic hypoplasia: “immunodeficiency”  
recurrent infections  
Cognitive impairment  
Hypoparathyroidism, hypocalcemia  
22q11 microdeletions  
High risk for psychiatric disorders |
| **Prader-Willi Syndrome** | Lack of expression of genes on paternal chromosome 15q11-13 due to deletion, maternal uniparental disomy of chromosome 15, or imprinting defect | 1:10,000             | "H2O": Hypotonia and weakness, Hypogonadism, obsessive Hyperphagia, Obesity  
Short stature, almond-shaped eyes, small hands and feet with tapering of fingers  
Developmental delay (variable)  
Hypopigmentation, type 2 DM |
| **Angelman Syndrome** | Lack of expression of genes on maternal chromosome 15q11-13 due to deletion or inactivation or paternal uniparental disomy |                      | Ataxia with severe intellectual disability, seizures, tremulousness, hypotonia  
Midface hypoplasia, fair hair, uncontrollable laughter |
| **CHARGE Syndrome** | 2/3 of children with CHARGE have been found to have a CHD7 mutation on chromosome 8 |                      | "CHARGE"  
C Coloboma  
H congenital Heart disease  
A choanal Atresia  
R mental Retardation  
G GU anomalies  
E Ear anomalies |

**DUCHENNE MUSCULAR DYSTROPHY**

**Epidemiology**
- 1:4,000 males

**Etiology**
- one type of muscular dystrophy characterized by progressive skeletal and cardiac muscle degeneration
- X-linked recessive: 1/3 spontaneous mutations, 2/3 inherited mutations
- missing structural protein (dystrophin) → muscle fibre fragility → fibre breakdown → necrosis and regeneration

**Clinical Presentation**
- proximal muscle weakness by age 3, positive Gower’s sign, waddling gait, toe walking
- pseudohypertrophy of calf muscles (muscle replaced by fat) and wasting of thigh muscles
- decreased reflexes
- non-progressive delayed motor and cognitive development (dysfunctional dystrophin in brain)
- cardiomyopathy

**Diagnosis**
- molecular genetic studies of dystrophin gene (DMD) (first line)
- family history (pedigree analysis)
- increased CK (50-100x normal) and lactate dehydrogenase
- elevated transaminases
- muscle biopsy, EMG

**Management**
- supportive (e.g. physiotherapy, wheelchairs, braces), prevent obesity
- cardiac health monitoring and early intervention
- bone health monitoring and intervention (vitamin D, bisphosphonates)
- steroids (e.g. prednisone or deflazacort)
- surgical (for scoliosis)
- gene therapy trials underway

**Complications**
- patient usually wheelchair-bound by 12 yr of age
- early flexion contractures, scoliosis, osteopenia of immobility, increased risk of fracture
- death due to pneumonia/respiratory failure or CHF in 2nd-3rd decade

**Metabolic Diseases**
- inherited disorders of metabolism; often autosomal recessive
- infants and older children may present with FTT or developmental delay
- universal newborn screening in Ontario includes metabolic disorders

**Metabolic disease must be ruled out in any newborn who becomes acutely ill after a period of normal behaviour and development or with a family history of early infant death even if the newborn screen is negative**
Table 21. Metabolic Disorders

<table>
<thead>
<tr>
<th>Examples of Conditions</th>
<th>Organic and Amino Acid Disorders</th>
<th>Carbohydrate Disorders</th>
<th>Fatty Acid Disorders</th>
<th>Organelle Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PKU</td>
<td></td>
<td></td>
<td>Mucopolysaccharidosis</td>
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<td></td>
<td>Tyrosinemia</td>
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<td>Congenital disorders of glycosylation</td>
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<td></td>
<td>Homocystinuria</td>
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<td>Lyssosomal storage diseases: Hurler’s, Niemann-Pick, Tay-Sachs, Gaucher, Fabry, Krabbe</td>
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<td></td>
<td>MSUD</td>
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<td></td>
<td>Alkaptonuria</td>
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<td></td>
<td>Urea cycle defects</td>
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<tr>
<td>Clinical Manifestations</td>
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<tr>
<td></td>
<td>Irritability, lethargy, poor feeding</td>
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<td></td>
<td>Seizures</td>
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<td></td>
<td>Intellectual disability</td>
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<td></td>
<td>Vomiting and acidosis after feeding initiation</td>
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<td></td>
<td>Sweet-smelling urine (MSUD)</td>
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<td>Laboratory Findings</td>
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<td></td>
<td>Hypoglycemic hyperammonemia, high anion gap (organic acidemia)</td>
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<td></td>
<td>Normoglycemic hyperammonemia, normal anion gap (urea cycle defects)</td>
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<td></td>
<td>Galactosemia</td>
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<td></td>
<td>GSDs: von Gierke’s, Pompe’s, Cori’s, Andersen, McArdle</td>
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<td></td>
<td>MCAD deficiency</td>
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<td></td>
<td>Carnitine deficiency</td>
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<tr>
<td>Physical Exam</td>
<td>Hypotonia/hypertonia</td>
<td></td>
<td>Hepatomegaly</td>
<td>Dyssmorphic facial features</td>
</tr>
<tr>
<td></td>
<td>Microcephaly, musty odour, eczema, hypopigmentation (PKU)</td>
<td></td>
<td>Hypotonia</td>
<td>Macrocephaly (Tay-Sachs, Hurler’s)</td>
</tr>
<tr>
<td></td>
<td>Dark urine, pigmented sclerae, arthralgias (alkaptonuria)</td>
<td></td>
<td></td>
<td>Hepatosplenomegaly (not Tay-Sachs)</td>
</tr>
<tr>
<td></td>
<td>Lens subluxation, marfanoid appearance (homocystinuria)</td>
<td></td>
<td></td>
<td>Cherry-red spot on macula (Niemann-Pick, Tay-Sachs, Gaucher’s)</td>
</tr>
<tr>
<td></td>
<td>Infantile cataracts (galactosemia)</td>
<td>Hepatomegaly</td>
<td></td>
<td>Corneal clouding (Hurler’s)</td>
</tr>
<tr>
<td></td>
<td>Hepatomegaly</td>
<td>Muscle weakness/cramping</td>
<td></td>
<td>Infantile cataract (Fabry)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Peripheral neuropathy (Fabry, Krabbe)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Spasticity</td>
</tr>
</tbody>
</table>

Initial Investigations
- important to send lab studies at initial presentation in order to facilitate immediate diagnosis and treatment
- check newborn screening results
- electrolytes, ABGs (calculate anion gap, rule out acidosis)
- CBC with differential and smear
- blood glucose (hypoglycemia seen with organic acidemia, fatty acid oxidation defects, and GSDs)
- lactate, ammonium (hyperammonemia with urea cycle defects), plasma Ca\(^{2+}\) and Mg\(^{2+}\)
- routine urinalysis: ketonuria must be investigated
- carnitine levels with acylcarnitine profile
- others: urate, urine nitroprusside, plasma amino acid screen, urine organic acids, CSF glycine, free fatty acids (3-β-hydroxybutyrate ratio >4 in fatty acid oxidation defect)
- storage diseases: urine mucopolysaccharide and oligosaccharide screen

Treatment
- varies according to inborn error of metabolism
- dietary restrictions, supplementation, enzyme replacement therapy, gene therapy, liver transplant, stem cell transplant

PHENYLKETONURIA

Epidemiology
- 1:10,000; autosomal recessive disease

Etiology
- deficiency of phenylalanine hydroxylase prevents conversion of phenylalanine to tyrosine leading to build up of toxic metabolites
- mothers who have PKU may have infants with congenital abnormalities

Clinical Presentation
- baby is normal at birth, then develops a musty odour, eczema, hypertonia, tremors, and mental retardation
- hypopigmentation due to low tyrosine (fair hair, blue eyes)

Management
- PKU screening at birth
- dietary restriction of phenylalanine starting within the first 10 d of life
- duration of dietary restriction controversial – lifelong or until end of puberty; should be resumed during pregnancy to maintain normal phenylalanine levels
GALACTOSEMIA

Epidemiology
- 1:60,000; autosomal recessive disease

Etiology
- most commonly due to deficiency of galactose-1-phosphate uridyltransferase leading to an inability to process lactose/galactose

Clinical Presentation
- signs of liver and renal failure, jaundice, FTT, and cataracts with ingestion of lactose/galactose

Management
- elimination of galactose from the diet (e.g. dairy, breast milk)
- most infants are fed a soy-based diet

Complications
- increased risk of sepsis, especially E. coli
- if the diagnosis is not made at birth, liver and brain damage may become irreversible

Hematology

Approach to Anemia

Figure 10. Approach to anemia

Physiologic Anemia
- high Hb (>170 g/L) and reticulocyte count at birth is caused by a hypoxic environment in utero
- after birth, levels start to fall due to shorter fetal RBC lifespan, decreased RBC production (during first 6-8 wk of life, there is virtually no erythropoiesis due to new O₂ rich environment), and increasing blood volume secondary to growth
- lowest levels about 100 g/L at 8-12 wk age (earlier and more exaggerated in premature infants); levels rise spontaneously with activation of erythropoiesis
- usually no treatment required

Iron Deficiency Anemia
- most common cause of childhood anemia
- full term infants exhaust iron reserves by 6 mo of age
- premature infants have lower reserves, therefore exhausted by 2-3 mo of age
- common diagnosis between 6 mo-3 yr and 11-17 yr due to periods of rapid growth and increased iron requirements; adolescents also have poor diet and menstrual losses

Etiology
- children at risk (premature, LBW, low SES, etc.)
- dietary risk factors: whole cow milk in first year of life
• age >6 mo: <2 servings/d of iron-fortified cereal, red meat, or legumes
• age <12 mo: use of low-iron formula (<10 mg/L), primary diet of cow, goat, or soy milk
• age 1-5 yr: >16-20 oz/d of non-fortified milk
• blood loss
  ▪ iatrogenic: repeated blood sampling (especially in hospitalized neonates)
  ▪ allergic: cow milk protein-induced colitis

**Clinical Manifestation**

• usually asymptomatic until marked anemia, pallor, fatigue, pica (eating non-food materials), tachycardia, systolic murmur, angular cheilitis, koilonychias

**Investigations**

• CBC: low Hb, MCV, and MCH, reticulocyte count normal or high (absolute number low)
  ▪ Mentzer index (MCV/RBC) can help distinguish iron deficiency anemia from thalassemia
    ▪ ratio <13 suggests thalassemia; ratio >13 suggests iron deficiency
  ▪ blood smear: hypochromic, microcytic RBCs, pencil shaped cells, poikilocytosis
  ▪ iron studies: low ferritin, other (low iron, high total iron binding capacity, high transferrin, low transferrin saturation)
  ▪ initial therapy: trial of iron

**Prevention**

• breastfed term infants: begin iron supplementation (1 mg/kg/d) at 4-6 mo, continuing until able to eat ≥2 feeds/d of iron-rich foods
• non-breastfed (<50% of diet) term infants: give iron-fortified formula from birth
• premature infants: give iron supplements from 1 mo through to 1 yr of age
• no cow’s milk until 9-12 mo, early introduction of red meat and iron-rich vegetables: total daily iron should be 11 mg (age 6-12 mo), 7 mg (age 1-3 yr)
• universal screening of Hb levels recommended at 9 mo

**Management**

• encourage diverse, balanced diet, limit homogenized milk to 16-20 oz/d
• oral iron therapy: 6 mg/kg/d elemental iron, divided bid to tid, for 3 mo
  ▪ increased reticulocyte count in 2-3 d (peaks day 5-7)
  ▪ increased hemoglobin in 4-30 d
  ▪ repletion of iron stores in 1-3 mo
  ▪ repeat hemoglobin levels after 1 mo of treatment
• poor response to oral iron therapy: non-compliance, medication intolerance, ongoing blood loss, IBD, celiac disease, incorrect diagnosis

**Complications**

• can cause irreversible effects on development if untreated (behavioural and intellectual deficiencies)
• angular cheilitis, glossitis, koilonychia (spoon nails)

**Vitamin K Deficiency**

• hemorrhagic disease of the newborn due to relative deficiencies of vitamin K-dependent coagulation factors
  ▪ generalized bleeding; GI/intracranial hemorrhage
• IM injection at birth, can also be given orally (3 doses: at birth, 2-4 wk, 6-8 wk) but infants at higher risk of HDNB
• reason for administration at birth:
  ▪ human milk contains small amounts of vitamin K, and infants require ingestion of large volumes of human milk to promote GI bacterial colonization
  ▪ until few days after birth, susceptible to vitamin K deficiency

**Anemia of Chronic Disease**

• see Hematology, H16

**Sickle Cell Disease**

• see Hematology, H21
Thalassemia

- see Hematology, H19

Hereditary Spherocytosis

- see Hematology, H23

Glucose-6-Phosphate Dehydrogenase Deficiency

- see Hematology, H23

Bleeding Disorders

- see Hematology, H27

Table 22. Evaluation of Abnormal Bruising/Bleeding

<table>
<thead>
<tr>
<th></th>
<th>PFA</th>
<th>PT</th>
<th>PTT</th>
<th>VIII:C</th>
<th>vWF</th>
<th>Platelets</th>
<th>Fibrinogen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>N</td>
<td>N</td>
<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>von Willebrand Disease</td>
<td>↑</td>
<td>N</td>
<td>N or ↑</td>
<td>↓</td>
<td>↓</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>DIC</td>
<td>N or ↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
<td>N</td>
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<tr>
<td>Vitamin K Deficiency</td>
<td>N</td>
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<td>↑</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
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<td>Thrombocytopenia</td>
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<td>N</td>
<td>N</td>
<td>N</td>
<td>N</td>
<td>↓</td>
<td>N</td>
</tr>
</tbody>
</table>

DIC = disseminated intravascular coagulation; PFA = platelet function assay; VIII:C = Factor VIII coagulant activity; vWF = von Willebrand Factor

Immune Thrombocytopenic Purpura

Epidemiology
- most common cause of thrombocytopenia in childhood
- peak age: 2-6 yr, M=F
- incidence 5:100,000 children per year

Etiology
- caused by autoantibodies that bind to platelet membranes → Fc-receptor mediated splenic uptake → destruction of platelets

Clinical Presentation
- 50% present 1-3 wk after viral illness (URTI, chicken pox)
- sudden onset of petechiae, purpura, epistaxis in an otherwise well child
- clinically significant bleed in only 3% (severe bleed more likely with platelet count <10) with <0.5% risk of intracranial bleed
- no lymphadenopathy, no hepatosplenomegaly
- labs: thrombocytopenia with normal RBC, WBC
- bone marrow aspirate only if atypical presentation (≥1 cell line abnormal, hepatosplenomegaly)
- differential diagnosis: leukemia, drug-induced thrombocytopenia, HIV, infection (viral), autoimmune (SLE, ALPS)

Management
- observation vs. pharmacologic intervention highly debated; spontaneous recovery in >70% of cases within 3 mo
- treatment with IVIg or prednisone if mucosal or internal bleeding, platelets <10, or at risk of significant bleeding (surgery, dental procedure, concomitant vasculitis or coagulopathy)
- life-threatening bleed: additional platelet transfusion ± emergency splenectomy
- persistent (>3-12 mo) or chronic (>12 mo): re-evaluate; treat if symptoms persist
- supportive: avoid contact sports and ASA/NSAIDs

Hemophilia

- see Hematology, H31
von Willebrand’s Disease

- see Hematology, H30

Oncology

- cancer is the second most common cause of death after injuries in children after 1 yr of age
- cause is rarely known, but increased risk for children with: chromosomal syndromes (e.g. Trisomy 21), prior malignancies, neurocutaneous syndromes, immunodeficiency syndromes, family history, exposure to radiation, chemicals, biologic agents
- leukemias are the most common type of pediatric malignancy (30%) followed by brain tumours (25%), and lymphomas (15%)
- some malignancies are more prevalent in certain age groups
  - newborns: neuroblastoma, Wilms’ tumour, retinoblastoma
  - infancy and childhood: leukemia, neuroblastoma, CNS tumors, Wilms’ tumour, retinoblastoma
  - adolescence: lymphoma, gonadal tumours, germ cell tumours, bone tumours
- unique treatment considerations in pediatrics because radiation, chemotherapy, and surgery can impact growth and development, endocrine function, and fertility
- good prognosis: treatments have led to remarkable improvements in overall survival and cure rates for many pediatric cancers (>80%)

Lymphadenopathy

Clinical Presentations

- features of malignant lymphadenopathy: firm, discrete, non-tender, enlarging, immobile ± suspicious mass/imaging findings ± constitutional symptoms
- fluctuance, warmth, or tenderness are more suggestive of benign nodes (infection)

Differential Diagnosis

- infection
  - viral: URTI, EBV, CMV, adenovirus, HIV
  - bacterial: S. aureus, GAS, anaerobes, Mycobacterium (e.g. TB), cat scratch disease (Bartonella)
    - other: fungal, protozoan, Rickettsia
  - autoimmune: rheumatoid arthritis, SLE, serum sickness
  - malignancy: lymphoma, leukemia, metastatic solid tumours
  - storage diseases: Niemann-Pick, Gaucher’s
  - other: sarcoidosis, Kawasaki disease, histiocytoses

Investigations

- generalized lymphadenopathy
  - CBC and differential, blood culture
  - uric acid, LDH
  - ANA, RF, ESR
  - EBV/CMV/HIV serology
  - toxoplasma titre
  - fungal serology
  - CXR
  - TB tests
  - biopsy
- regional lymphadenopathy
  - period of observation if asymptomatic
  - trial of oral antibiotics
  - ultrasonad
  - biopsy (especially if persistent >6 wk and/or constitutional symptoms)

Leukemia

- see Hematology, H37

Epidemiology

- mean age of diagnosis 2-5 yr but can occur at any age
- heterogeneous group of diseases
  - ALL (80%)
  - AML (15%)
  - CML (<5%)
- children with DS are 15x more likely to develop leukemia

Clinical Presentation

- infiltration of leukemic cells into bone marrow results in bone pain and bone marrow failure (anemia, neutropenia, thrombocytopenia)
- infiltration into tissues results in lymphadenopathy, hepatosplenomegaly, CNS manifestations, testicular disease

Most common cause of acute bilateral cervical LAD is viral illness
• fever, fatigue, weight loss, bruising, and easy bleeding
• hyperleukocytosis (total WBC >100 x 10^9/L) is a medical emergency
  ▪ presents clinically with respiratory or neurological distress caused by hyperviscosity of blood and leukostasis
  ▪ risk of ICH, pulmonary leukostasis syndrome, tumour lysis syndrome
• management: fluids, allopurinol/rasburicase, fresh frozen plasma/platelets to correct thrombocytopenia, induction chemotherapy, avoid transfusing RBCs unless symptomatic (and then use very small volumes)

Management
• combination chemotherapy using non-cross resistant chemotherapy agents, allogeneic stem cell transplantation for high-grade or recurrent disease
• supportive care and management of treatment complications
  ▪ febrile neutropenia: see Infectious Diseases, ID45
  ▪ tumour lysis syndrome: see Hematology, H52

Prognosis
• 80-90% 5 yr event-free survival for ALL, 50-60% 5-yr survival for AML
• patients are stratified into standard risk and high risk based on WBC and age; other prognostic factors include presence of CNS/testicular disease, immunophenotype, cytogenetics, and initial response to therapy (most important prognostic variable)

Lymphoma
• see Hematology, H44

Epidemiology
• Hodgkin lymphoma: incidence is bimodal, peaks at ages 15-34 and >50 yr old
• non-Hodgkin lymphoma: incidence peaks at 7-11 yr

Clinical Presentation
• Hodgkin lymphoma
  ▪ most common presentation is persistent, painless, firm, cervical or supraclavicular lymphadenopathy
  ▪ can present as persistent cough or dyspnea (secondary to mediastinal mass) or less commonly as splenomegaly, axillary, or inguinal lymphadenopathy
  ▪ constitutional symptoms in 30% of children
  ▪ lymph nodes become sequentially involved as disease spreads
• non-Hodgkin lymphoma
  ▪ generally categorized into lymphoblastic, large cell, and Burkitt’s/Burkitt’s-like lymphoma
  ▪ rapidly growing tumour with distant metastases (unlike adult non-Hodgkin lymphoma)
  ▪ signs and symptoms related to disease site: most commonly abdomen, chest (mediastinal mass), head and neck region

Management
• Hodgkin lymphoma
  ▪ combination chemotherapy and radiation
  ▪ aimed at limiting cumulative doses of anthracyclines (toxic to heart) and alkylators (risk of second malignancy, infertility) and limiting dose and field of radiation
  ▪ increasing role for use of PET scanning to assess early disease response and plan therapy
• non-Hodgkin lymphoma
  ▪ combination chemotherapy
  ▪ no added benefit of radiation in pediatric protocols

Prognosis
• Hodgkin lymphoma: >90% 5 yr survival
• non-Hodgkin lymphoma: 75-90% 5 yr survival

Brain Tumours
• see Neurosurgery, NS37

Wilms’ Tumour (Nephroblastoma)

Epidemiology
• usually diagnosed between 2-5 yr; M=F
  ▪ most common primary renal neoplasm of childhood
  ▪ 5-10% of cases both kidneys are affected (simultaneously or in sequence)

Differential Diagnosis
• hydronephrosis, polycystic kidney disease, renal cell carcinoma, neuroblastoma
Clinical Presentation
- 80% present with asymptomatic, unilateral abdominal mass
- may also present with HTN, gross hematuria, abdominal pain, vomiting
- may have pulmonary metastases at time of diagnosis (respiratory symptoms)

Associated Congenital Abnormalities
- WAGR syndrome (Wilms' tumour, Aniridia, Genital anomalies, mental Retardation) with 11p13 deletion:
  - characterized by enlargement of body organs (especially tongue), hemihypertrophy, renal medullary cysts, and adrenal cytomegaly
  - also at increased risk for developing hepatoblastoma, and less commonly adrenocortical tumours, neuroblastomas, and rhabdomyosarcomas
- Denys-Drash syndrome: characterized by gonadal dysgenesis and nephropathy leading to renal failure

Management
- staging ± nephrectomy
- chemotherapy, radiation for higher stages

Prognosis
- 90% long-term survival

Neuroblastoma

Epidemiology
- most common cancer occurring in first year of life
- neural crest cell tumour arising from sympathetic tissues (neuroblasts)

Clinical Presentation
- can originate from any site in sympathetic nervous system, presenting as mass in neck, chest, or abdomen (most common site is adrenal gland)
- signs and symptoms of disease vary with location of tumour:
  - thoracic: dyspnea, Horner's syndrome
  - abdominal: palpable mass
  - spinal cord compression
- metastases are common at presentation (>50% present with advanced stage disease):
  - usually to bone or bone marrow (presents as bone pain, limp)
  - can also present with periorbital ecchymoses, abdominal pain, emesis, fever, weight loss, anorexia, hepatomegaly, "blueberry muffin" skin nodules
  - paraneoplastic: HTN, palpitations, sweating (from excessive catecholamines), diarrhea, FTT (from vasoactive intestinal peptide secretion), opsomyoclonus
- diagnostic criteria (either of the following):
  - unequivocal histologic diagnosis from tumour tissue biopsy
  - evidence of metastasis to bone marrow ("rosettes") on aspirate analysis, with concomitant elevation of urine or serum catecholamine metabolite (VMA, HVA) levels

Management
- depends on prognostic factors and may include combination of: surgery, radiation, chemotherapy, autologous stem cell transplantation, immunotherapy

Prognosis
- prognosis is often poor due to late detection
- good prognostic factors:
  - "age and stage" are important determinants of better outcome: 12-18 mo, stage I, II, IV-S disease ("S" designates a "Special" classification only pertaining to infants)
  - primary site: posterior medias tinum and neck
  - low serum ferritin
  - specific histology
  - tumour cell markers: aneuploidy, absent MYCN oncogene amplification

Bone Tumours
- see Orthopedics, OR46
Infectious Diseases

Fever

Definition
- fever: a practical definition is >38°C/100.4°F oral or rectal
- fever without a source/focus: acute febrile illness (typically <10 d duration) with no cause of fever even after careful history and physical
- fever of unknown origin: daily or intermittent fevers for at least 2 consecutive weeks of uncertain cause after careful history and physical, and initial laboratory assessment

Etiology
- infectious: anatomic approach (CNS, ears, upper and lower respiratory tract, GI, GU, skin, soft tissue, bones and joints, etc.)
- inflammatory: mainly autoimmune (Kawasaki disease, JIA, IBD, SLE, etc.)
- malignancy: childhood cancers (leukemia, lymphoma, neuroblastoma, etc.)
- miscellaneous: dehydration, drugs and toxins, post-immunization, familial dysautonomia, factitious disorder, etc.

Diagnosis
- history: duration, height and pattern of fever, associated symptoms, exposures, constitutional symptoms, recent antipyretic use, ethnic or genetic background, day care, sick contacts, travel, tick bites, age of child
- physical exam: toxic vs. non-toxic, vitals, growth, complete exams of the skin, HEENT, chest, abdomen, lymph nodes, genitalia
- investigations: guided by history, physical exam, and clinical suspicion

Evaluation of Neonates and Infants with Fever
- several protocols exist that attempt to identify neonates and young infants at low risk of serious bacterial infection (e.g. Rochester Criteria)
  - such protocols are not as sensitive in the 1-28 d age group; therefore, febrile neonates should be considered high risk regardless of clinical presentation and laboratory findings

Management
- admit to hospital if appropriate
- treat the source if known
- replace fluid losses (e.g. from vomiting, diarrhea, etc.); maintenance fluid needs are higher in febrile child
- reassure parents that most fevers are benign and self-limited
- antipyretics (acetaminophen and/or ibuprofen) are not necessary in most cases, but can be given if child is uncomfortable

Figure 11. Approach to the febrile child

Rochester Criteria – Developed to Identify Infants ≤60 d of Age with Fever at Low Risk of Serious Bacterial Infection

<table>
<thead>
<tr>
<th>Clinically</th>
<th>Well</th>
</tr>
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<tbody>
<tr>
<td>WBC Count</td>
<td>5-15 x 10⁹/L</td>
</tr>
<tr>
<td>Bands</td>
<td>&lt;1.5 x 10⁹/L</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>&lt;10 WBC/HPF</td>
</tr>
<tr>
<td>Stool (if diarrhea)</td>
<td>&lt;5 WBC/HPF</td>
</tr>
<tr>
<td>Past Health</td>
<td>Born &gt;37 wk</td>
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<tr>
<td>Home with/before mom</td>
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</tr>
<tr>
<td>No hospitalizations</td>
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<tr>
<td>No prior antibiotic use</td>
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</tr>
<tr>
<td>No prior treatment for unexplained hyperbilirubinemia</td>
<td></td>
</tr>
<tr>
<td>No chronic disease</td>
<td></td>
</tr>
</tbody>
</table>

NOTES
1. Full Septic Workup (SWU) – blood C&S, CBC and differential, urine R&M, C&S, LP, CXR if respiratory symptoms, stool C&S if GI symptoms
2. Follow-up is crucial – if adequate follow-up is not assured, a more aggressive diagnostic and therapeutic approach may be indicated
3. Low-risk (Rochester) criteria
4. Considerable practice variation exists in terms of empiric antibiotic treatment
5. Important principles – the younger the child, the greater the difficulty to clinically assess the degree of illness
Acute Otitis Media

Definition
All of:
1. presence of middle ear effusion
2. presence of middle ear inflammation
3. acute onset of symptoms of middle ear effusion and inflammation

Epidemiology
- 60-70% of children have at least 1 episode of AOM before 3 yr of age
- 18 mo-6 yr most common age group
- peak incidence January to April
- one third of children have had ≥3 episodes by age 3

Etiology
- *H. influenzae* (non-typeable): >50% of refractory AOM
- *S. pneumoniae*: 32% of cases (incidence decreasing due to pneumococcus vaccine)
- *M. catarrhalis*: 14% of cases
- *S. aureus* and *S. pyogenes* (all β-lactamase producing)
- anaerobes (newborns)
- Gram-negative enterics (infants)
- viral

Predisposing Factors
- Eustachian tube dysfunction/obstruction
  - swelling of tubal mucosa: URTI, allergic rhinitis, chronic rhinosinusitis
  - obstruction/infiltration of Eustachian tube ostium: adenoid hypertrophy (not due to obstruction but by maintaining a source of infection), barotrauma (sudden changes in air pressure)
  - inadequate tensor palatini function: cleft palate (even after repair)
  - abnormal Eustachian tube: DS (horizontal position of Eustachian tube), Crouzon syndrome, cleft palate, and Apert syndrome
- disruption of action of
  - cilia of Eustachian tube: Kartagener’s syndrome
  - mucus secreting cells
  - capillary network that provides humoral factors, neutrophils, phagocytic cells
- immunosuppression/deficiency due to chemotherapy, steroids, DM, hypogammaglobulinemia, CF

Risk Factors
- bottle feeding, pacifier use
- second-hand smoke
- crowded living conditions (day care/group child care facilities) or sick contacts
- male
- family history
- craniofacial abnormalities
- immunodeficiency
- ethnicity

Pathogenesis
- obstruction of Eustachian tube → air absorbed in middle ear → negative pressure (an irritant to middle ear mucosa) → edema of mucosa with exudate/effusion → infection of exudate from nasopharyngeal secretions

Clinical Features
- triad of otalgia, fever (especially in younger children), and conductive hearing loss
- rarely tinnitus, vertigo, and/or facial nerve paralysis
- otorrhea if tympanic membrane perforated
- infants/toddlers: ear-tugging (this alone is not a good indicator of pathology), hearing loss, balance disturbances (rare), irritable, poor sleeping, vomiting and diarrhea, anorexia
- otoscopy of TM: hyperemia, bulging, pus may be seen behind TM, loss of landmarks (e.g. handle and long process of malleus not visible)

Diagnosis
- bulging TM (based on pneumatic otoscopy or tympanometry) is required for the diagnosis of AOM

Management
- 1st line
  - amoxicillin 75-90 mg/kg/d divided into two doses: safe, effective, and inexpensive
  - if penicillin allergic: macrolide (clarithromycin, azithromycin – high resistance), trimethoprim-sulphamethoxazole (Bactrim*)
• 2nd line
  ▪ amoxicillin-clavulanic acid (Clavulin®)
  ▪ cephalosporins: cefuroxime axetil (Ceftin®), ceftriaxone (Rocephin®), cepaclor (Ceclor®), cefixime (Suprax®)
  ▪ AOM deemed unresponsive if clinical signs/symptoms and otoscopic findings persist beyond 48 h of antibiotic treatment
• symptomatic therapy: antipyretics/analgesics (e.g. acetaminophen), decongestants (may relieve nasal congestion but does not treat AOM)
• prevention: parent education about risk factors, pneumococcal and influenza vaccines, surgery (e.g. tympanostomy tubes)
  ▪ choice of surgical therapy for recurrent AOM depends on whether local factors (Eustachian tube dysfunction) are responsible (use ventilation tubes), or regional disease factors (tonsillitis, adenoid hypertrophy, sinusitis) are responsible

Complications
• extracranial: hearing loss and speech delay (secondary to persistent middle ear effusion), TM perforation, extension of suppurative process to adjacent structures (mastoiditis, petrositis, labyrinthitis), cholesteatoma, facial nerve palsy, middle ear atelectasis, ossicular necrosis, vestibular dysfunction
• intracranial: meningitis, epidural and brain abscess, subdural empyema, lateral and cavernous sinus thrombosis, carotid artery thrombosis

Otitis Media with Effusion

Definition
• presence of fluid in the middle ear without signs or symptoms of ear infection

Epidemiology
• most common cause of pediatric hearing loss
• not exclusively a pediatric disease
• follows AOM frequently in children
• middle ear effusions have been shown to persist following an episode of AOM for 1 mo in 40% of children, 2 mo in 20%, and >3 mo in 10%

Risk Factors
• same as AOM

Clinical Features
• conductive hearing loss ± tinnitus
• fullness – blocked ear
• ± pain, low grade fever
• otoscopy of TM
  ▪ discoloration – amber or dull grey
  ▪ meniscus fluid level behind TM
  ▪ air bubbles
  ▪ retraction pockets/TM atelectasis
  ▪ flat tympanogram
  ▪ most reliable finding with pneumatic otoscopy is immobility

Treatment
• expectant: 90% resolve by 3 mo
• document hearing loss with audiogram (see Otolaryngology Figure 16B and Figure 17B, OT10-11)
• no statistical proof that antihistamines, decongestants, antibiotics clear disease faster
• surgery: myringotomy ± ventilation tubes ± adenoidectomy (if enlarged or on insertion of second set of tubes a few months after first set falls out)
• ventilation tubes to equalize pressure and drain ear

Complications of OME
• hearing loss, speech delay, learning problems in young children
• chronic mastoiditis
• ossicular erosion
• cholesteatoma especially when retraction pockets involve pars flaccida
• retraction of tympanic membrane, atelectasis, ossicular fixation

Gastroenteritis
• see Gastroenterology, P36

HIV Infection
• see Infectious Diseases, ID28
<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen(s)</th>
<th>Incubation Period</th>
<th>Communicability</th>
<th>Mode of Transmission</th>
<th>Rash Description</th>
<th>Associated Features</th>
<th>Management</th>
<th>Outcomes and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Infectiosum (i.e. Fifth Disease)</td>
<td>Parvovirus B19</td>
<td>4-14 d</td>
<td>Low risk of transmission once symptomatic</td>
<td>Respiratory secretions or infected blood</td>
<td>Appearance: uniform, erythematous maculopapular 'lacy' rash Timing: 10-17 d after symptoms (immune response) Distribution: bilateral cheeks ('slapped cheeks') with circumoral sparing; may affect trunk and extremities</td>
<td>Initial 7-10 d of flu-like illness and fever Rash may be warm, non-tender, and pruritic Less common presentations include 'gloves and socks syndrome' or STAR complex (sore throat, arthritis, rash)</td>
<td>Supportive</td>
<td>Rash fades over days to week, but may reappear months later with sunlight, exercise Aplastic crisis</td>
</tr>
<tr>
<td>Gianotti-Crosti Syndrome (i.e. Papular Acrodermatitis)</td>
<td>EBV and Hep B (majority)</td>
<td>Variable</td>
<td>None</td>
<td>Appearance: asymptomatic symmetric papules Distribution: face, cheeks, extensor surfaces of the extremities, spares trunk</td>
<td>Appearance: vesicles and pustules on an erythematous base Distribution: acral</td>
<td>Viral prodrome May have lymphadenopathy and/or hepatosplenomegaly</td>
<td>Supportive Pain control</td>
<td>Resolves in 3-12 wk</td>
</tr>
<tr>
<td>Hand, Foot, and Mouth Disease</td>
<td>Coxsackie group A</td>
<td>3-5 d</td>
<td>Likely 1-7 d after symptoms but may be up to months</td>
<td>Direct and indirect contact with infected bodily fluids, fecal-oral</td>
<td>Appearance: vesicles and pustules on an erythematous base Distribution: acral</td>
<td>Enanthem: vesicles in the POSTERIOR oral cavity (pharynx, tongue)</td>
<td>Supportive</td>
<td>Mainly dehydration</td>
</tr>
<tr>
<td>Herpes Simplex</td>
<td>HSV 1,2</td>
<td>1-26 d</td>
<td>Direct contact, often through saliva for HSV-1 and sexual contact for HSV-2</td>
<td>Grouped vesicles on an erythematous base</td>
<td>Enanthem: vesicles/erosions in the ANTERIOR oral cavity (buccal mucosa, tongue) May present with herpetic whitlow (autoinoculation)</td>
<td>Mainly supportive Consider oral or topical antivirals</td>
<td>Local: secondary skin infections, keratitis, gingivostomatitis CNS: encephalitis Disseminated hepatitis, DIC Eczema herpeticum</td>
<td></td>
</tr>
<tr>
<td>Kawasaki Disease</td>
<td>See P94</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Measles</td>
<td>Morbillivirus</td>
<td>8-13 d</td>
<td>4 d before and after rash</td>
<td>Airborne</td>
<td>Appearance: erythematous maculopapular Timing: 3 d after start of symptoms Distribution: starts at hairline and spreads downwards with sparing of palms and soles</td>
<td>Prodome of cough, coryza, conjunctivitis (3 Cs) Enanthem: Koplik’s spots 1-2 d before rash Desquamation Positive serology for measles IgM</td>
<td>Infected: supportive Unimmunized contacts: measles vaccine within 72 h of exposure or IgG within 6 d of exposure Respiratory isolation, report to Public Health Prevention: MMR vaccine</td>
<td>Secondary bacterial infections: AOM, sinusitis, pneumonia Encephalitis Rare: myocarditis, pencearditis, thrombocytopenia, Stevens-Johnson syndrome, GN, subacute sclerosing panencephalitis</td>
</tr>
</tbody>
</table>
### Table 23. Common Infectious Pediatric Exanthems (continued)

<table>
<thead>
<tr>
<th>Disease</th>
<th>Pathogen(s)</th>
<th>Incubation Period</th>
<th>Communicability</th>
<th>Mode of Transmission</th>
<th>Rash</th>
<th>Associated Features</th>
<th>Management</th>
<th>Outcomes and Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Specific Enteroviral Exanthems</td>
<td>Enteroviruses</td>
<td>Variable</td>
<td>Variable</td>
<td>Direct and indirect contact with infected bodily fluids</td>
<td>Polymorphous rash (macules, papules, vesicles, petechiae, urticaria)</td>
<td>Systemic involvement is rare, but possible</td>
<td>Supportive Diagnosis confirmed using viral cultures (NP and rectal swabs)</td>
<td>Self-limiting</td>
</tr>
<tr>
<td>Roseola</td>
<td>HHV 6</td>
<td>5-15 d</td>
<td>Unknown</td>
<td>—</td>
<td>Appearance: blanching, pink, maculopapular</td>
<td>High grade fever Common: irritability, anorexia, lymphadenopathy, erythematous TM and pharynx, Nagayama spots (erythematous papules on soft palate and uvula) Less common: cough, coryza, bulging fontanelles</td>
<td>Supportive</td>
<td>CNS: febrile seizures (10-25%), aseptic meningitis Thrombocytopenia</td>
</tr>
<tr>
<td>Rubella</td>
<td>Rubivirus</td>
<td>14-21 d</td>
<td>7 d before and after eruptions</td>
<td>Droplet</td>
<td>Appearance: pink, maculopapular Timing: 1-5 d after start of symptoms Distribution: starts on face and spreads to neck and trunk</td>
<td>Prodrome of low grade fever and occipital/retroauricular nodes STAR complex (sore throat, arthritis, rash) Positive serology for rubella IgM</td>
<td>Infected: supportive Prevention: MMR vaccine Report to Public Health</td>
<td>Excellent prognosis with acquired disease Arthritis may last days to weeks Encephalitis Irreversible defects in congenitally infected patients (i.e. congenital rubella syndrome)</td>
</tr>
<tr>
<td>Scarlet Fever</td>
<td>See P59</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Varicella</td>
<td>Varicella zoster virus</td>
<td>0-21 d</td>
<td>1-2 d pre-eruptions and 5 d post-eruption</td>
<td>Mainly airborne, but also through direct contact with vesicle fluid Timing: 1-3 d after start of symptoms Distribution: generalized</td>
<td>Appearance: groups of skin lesions, polymorphic, from macules to papules to vesicles to crusts</td>
<td>Significant pruritis Enanthem: vesicular lesions which may become pustular or ulcerate</td>
<td>Supportive Avoid salicylates (due to risk of Reye syndrome) Consider antivirals Respiratory and contact isolation, report to Public Health Prevention: varicella vaccine</td>
<td>Skin: bacterial suprainfection, necrotizing fasciitis CNS: acute encephalitis and cerebellar ataxia Systemic: hepatitis, DIC Congenital varicella syndrome if intrapartum infection</td>
</tr>
</tbody>
</table>
Infectious Mononucleosis

Definition
- systemic viral infection caused by EBV with multivisceral involvement; often called “the great imitator”

Epidemiology
- peak incidence between 15-19 yr old
- ~50% of children in developed countries have a primary EBV infection by 5 yr old, but <10% of children develop clinical infection

Etiology
- EBV: a member of herpesviridae
- transmission is mainly through infected saliva (“kissing disease”) and sexual activity (less commonly); incubation period of 1-2 mo

Risk Factors
- infectious contacts, sexually active, multiple sexual partners in the past

History
- prodrome: 2-3 d of malaise, anorexia
- infants and young children: often asymptomatic or mild disease
- older children and adolescents: malaise, fatigue, fever, sore throat, abdominal pain (often LUQ), headache, myalgia

Physical Exam
- classic triad: febrile, generalized non-tender lymphadenopathy, pharyngitis/tonsillitis (exudative)
- ± hepatosplenomegaly
- ± periorbital edema, ± rash (urticarial, maculopapular, or petechial) – more common after inappropriate treatment with β-lactam antibiotics
- any “-itis” (including arthritis, hepatitis, nephritis, myocarditis, meningitis, encephalitis, etc.)

Investigations
- heterophil antibody test (Monospot® test)
  - 85% sensitive in adults and older children, but only 50% sensitive if <4 yr of age
  - false positive results with HIV, SLE, lymphoma, rubella, parvovirus
- EBV titres
- CBC and differential, blood smear: atypical lymphocytes, lymphocytosis, Downey cells ± anemia ± thrombocytopenia
- throat culture to rule out streptococcal pharyngitis

Management
- supportive: adequate rest, hydration, saline gargles, and analgesics for sore throat
- splenic enlargement is often not clinically apparent so all patients should avoid contact sports for 6-8 wk
- if airway obstruction secondary to nodal and/or tonsillar enlargement is present (especially younger children), admit for steroid therapy
- acyclovir does NOT reduce duration of symptoms or result in earlier return to school/work

Prognosis
- most acute symptoms resolve in 1-2 wk, though fatigue may last for months
- short-term complications: splenic rupture, Guillain-Barré syndrome

Infectious Pharyngitis/Tonsillitis

Definition
- inflammation of the pharynx, especially the tonsils if present, causing a sore throat

Etiology
- viral (~80%): adenoviruses, enteroviruses, coxsackie, upper respiratory tract viruses, EBV, CMV
- bacterial (~20%): mainly GAS, M. pneumoniae (older children), N. gonorrhoeae (sexually active), C. diphtheriae (unvaccinated)
- fungal: Candida

Epidemiology
- season: GAS pharyngitis more common in late winter or early spring; viral all year long
- age: GAS pharyngitis peak incidence at 5-12 yr of age and uncommon <3 yr; viral pharyngitis affects all ages

History
- GAS: sore throat (may be severe), fever, malaise, headache, abdominal pain, N/V, absence of other URTI symptoms
- viral: sore throat (often mild), conjunctivitis, cough, rhinorrhea, hoarseness, diarrhea, flu-like symptoms (fever, malaise, myalgias)
Physical Exam
- GAS: febrile, pharyngeal/tonsillar erythema and exudates, enlarged (>1 cm) and tender anterior cervical lymph nodes, palatal petechiae, strawberry tongue, scarlatiniform rash
- viral: afebrile, absent/mild tonsillar exudates, minor and non-tender adenopathy, viral exanthems

Investigations
- no single sign or symptom reliably identifies GAS as the causative organism in children with sore throat
- scores are used to predict if throat culture will be positive (e.g. McIsaac Criteria)
  - these score systems have not been found to be sensitive or specific enough to diagnose GAS in children and adolescents with sore throat
- suspected diagnosis of GAS pharyngitis should be confirmed with a rapid streptococcal antigen test and a follow-up throat culture if the rapid test is negative

Management
- antibiotics (for GAS/S. pyogenes)
  - penicillin V or amoxicillin or erythromycin (if penicillin allergy) x 10 d
  - can prevent rheumatic fever if given within 9 d of symptoms; does NOT alter risk of post-streptococcal GN
- supportive: hydration and acetaminophen for discomfort due to pain and/or fever
- follow-up: if uncomplicated course, no follow-up or post-antibiotic throat cultures needed
- prophylaxis: consider tonsillectomy for proven, recurrent streptococcal tonsillitis

Complications
- preventable with antibiotics: AOM, sinusitis, cervical adenitis, mastoiditis, retropharyngeal/peritonsillar abscess, sepsis
- immune-mediated complications: scarlet fever, acute rheumatic fever, post-streptococcal GN, reactive arthritis, pediatric autoimmune neuropsychiatric disorder associated with group A Streptococci (i.e. PANDAS)

SCARLET FEVER
- diffuse erythematous eruption
- delayed-type hypersensitivity reaction to pyrogenic exotoxin produced by GAS
- acute onset of fever, sore throat, strawberry tongue
- 24–48 h after pharyngitis, rash begins in the groin, axillae, neck, antecubital fossa; Pastia's lines may be accentuated in flexural areas
- within 24 h, sandpaper rash becomes generalized with perioral sparing, non-pruritic, non-painful, blanchable
- rash fades after 3-4 d, may be followed by desquamation
- treatment is penicillin, amoxicillin, or erythromycin x 10 d

RHEUMATIC FEVER
- inflammatory disease due to antibody cross-reactivity following GAS infection
- affects ~1:10,000 children in developed world; much more prevalent in developing nations; peak incidence at 5-15 yr of age
- mainly a clinical diagnosis based on Jones Criteria (revised)
  - requires 2 major OR 1 major and 2 minor PLUS evidence of preceding strep infection (history of scarlet fever, GAS pharyngitis culture, positive rapid Ag detection test, ASOTs)
- treatment: penicillin or erythromycin for acute course x 10 d, prednisone if severe carditis
- secondary prophylaxis with daily penicillin or erythromycin
- complications
  - acute: myocarditis, conduction system aberrations (sinus tachycardia, atrial fibrillation), valvulitis (acute MR), pericarditis
  - chronic: valvular heart disease (mitral and/or aortic insufficiency/stenosis), infectious endocarditis ± thromboembolic phenomenon
- onset of symptoms usually after 10-20 yr latency from acute carditis of rheumatic fever

POST-STREPTOCOCCAL GLOMERULONEPHRITIS
- most common in children aged 4-8 yr old; M>F
- antigen-antibody mediated complement activation with diffuse, proliferative GN
- occurs 1-3 wk following initial GAS infection (skin or throat)
- clinical presentation varies from asymptomatic, microscopic and macroscopic hematuria (coloured urine) to all features of nephritic syndrome (see P80)
- diagnosis is confirmed with elevated serum antibody titres against streptococcal antigens (ASOT, anti-DNAse B), low serum complement (C3)
- management
  - symptomatic: fluid and sodium restrictions; loop diuretics for HTN and edema
  - in severe cases, may require dialysis if renal function significantly impaired
  - treat with penicillin or erythromycin if evidence of persistent GAS infection
- 95% of children recover completely within 1-2 wk; 5-10% have persistent hematuria
Meningitis

Definition
• inflammation of the meninges surrounding the brain and spinal cord

Epidemiology
• peak age: 6-12 mo; 90% of cases occur in children <5 yr old

Etiology
• viral: enteroviruses, HSV
• bacterial: age-related variation in specific pathogens
• fungal and parasitic meningitis also possible
• most often due to hematogenous spread or direct extension from a contiguous site

Risk Factors
• unvaccinated
• immunocompromised: asplenia, DM, HIV, prematurity
• recent or current infections: AOM, sinusitis, orbital cellulitis
• neuroanatomical: congenital defects, dermal sinus, neurosurgery, cochlear implants, recent head trauma
• exposures: day care centres, household contact, recent travel

History
• signs and symptoms variable and dependent on age, duration of illness, and host response to infection
• infants: fever, lethargy, irritability, poor feeding, vomiting, diarrhea, respiratory distress, seizures
• children: fever, headache, photophobia, N/V, confusion, back/neck pain/stiffness, lethargy, irritability

Physical Exam
• infants: toxic, hypothermia, bulging anterior fontanelle, respiratory distress, apnea, petechial/purpuric rash, jaundice
• children: toxic, LOC, nuchal rigidity, Kernig's and Brudzinski's signs, focal neurologic findings, petechial/purpuric rash

Investigations
• blood work: CBC, electrolytes, Cr, BUN, glucose, C&S
• LP required for definitive diagnosis
• Gram stain, bacterial C&S, WBC count and differential, RBC count, glucose, protein concentration
• acid-fast stain if suspect TB
• PCR for specific bacteria if available (helpful if already treated with antibiotics)
• urinalysis and urine C&S in infants, Gram stain and culture of petechial/purpuric lesions
• HSV and enterovirus PCR if suspected

Table 24. CSF Findings of Meningitis

<table>
<thead>
<tr>
<th>Component</th>
<th>Normal Child</th>
<th>Normal Newborn</th>
<th>Bacterial Meningitis</th>
<th>Viral Meningitis</th>
<th>Herpes Meningitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>WBC (×10^6/µL)</td>
<td>0-6</td>
<td>0-30</td>
<td>&gt;1,000</td>
<td>100-500*</td>
<td>10-1,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(cloudy, xanthochromic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>0</td>
<td>2-3</td>
<td>&gt;50</td>
<td>&lt;40</td>
<td>&lt;50</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>2.2-4.4</td>
<td>1.8-6.7</td>
<td>&lt;1.66</td>
<td>&gt;1.66</td>
<td>&gt;1.66</td>
</tr>
<tr>
<td>Protein (mg/dL)</td>
<td>0.2-0.3</td>
<td>0.19-1.49</td>
<td>&gt;1.0</td>
<td>0.50-1.0</td>
<td>&gt;0.75</td>
</tr>
<tr>
<td>RBC (×10^6/µL)</td>
<td>0.2-0.2</td>
<td>0.2</td>
<td>0-10</td>
<td>0-2</td>
<td>10-50</td>
</tr>
</tbody>
</table>

*lymphocytes predominate


Management
• supportive care
  • preservation of adequate cerebral perfusion by maintaining normal BP and managing ↑ ICP
  • close monitoring of fluids, electrolytes, glucose, acid-base disturbances, coagulopathies
  • bacterial meningitis
    • if suspected or cannot be excluded, commence empiric antibiotic therapy while awaiting cultures or if LP contraindicated or delayed
    • adjuvant dexamethasone BEFORE antibiotic for Hib meningitis; consider for those >6 wk with pneumococcal meningitis
    • isolation with appropriate infection control procedures until 24 h after culture-sensitive antibiotic therapy
    • fluid restrict if any concern for SIADH
    • hearing test
    • report to Public Health; prophylactic antibiotics for close contacts of Hib and N. meningitidis meningitis

Signs of Meningismus
• BONK on the head
• Brudzinski’s sign
• Opisthotonos*
• Nuchal rigidity
• Kernig’s sign

*Opisthotonos: rigid spasm of the body, with the back fully arched and the heels and head bent back
### Table 25. Antibiotic Management of Bacterial Meningitis

<table>
<thead>
<tr>
<th>Age</th>
<th>Main Pathogens</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 28 d</td>
<td>GBS, <em>E. coli</em>, Listeria Other: Gram-negative bacilli</td>
<td>Ampicillin + cefotaxime</td>
</tr>
<tr>
<td>28 to 90 d</td>
<td>Overlap of neonatal pathogens and those seen in older children</td>
<td>Cefotaxime + Vancomycin (+ Ampicillin If immunocompromised)</td>
</tr>
<tr>
<td>&gt;90 d</td>
<td><em>S. pneumoniae</em>, <em>N. meningitidis</em></td>
<td>Ceftriaxone ± vancomycin</td>
</tr>
<tr>
<td></td>
<td></td>
<td>If Penicillin allergic: Vancomycin + Rifampin</td>
</tr>
</tbody>
</table>

- viral meningitis
  - mainly supportive (except for HSV)
  - acyclovir for HSV meningitis
  - report to Public Health
- prophylaxis: appropriate vaccinations significantly decrease incidence of bacterial meningitis (see *Routine Immunization*, P3)

### Complications
- mortality: neonate 15-20%, children 4-8%; pneumococcus > meningococcus > HIB
- acute: SIADH, subdural effusion/empyema, brain abscess, disseminated infection (osteomyelitis, septic arthritis, abscess), shock/DIC
- chronic: hearing loss, neuromotor/cognitive delay, learning disabilities, neurological deficit, seizure disorder, hydrocephalus

## Mumps

### Definition
- acute, self-limited viral infection that is most commonly characterized by adenitis and swelling of the parotid glands

### Epidemiology
- incidence in Ontario has declined since introduction of two-dose MMR vaccination schedule
- average of 25 reported cases per yr
- majority of reported cases in children between 5-10 yr of age

### Etiology
- mumps virus (RNA virus of the genus *Rubulavirus* in the *Paramyxoviridae* family)
- transmission via respiratory droplets, direct contact, fomites
- incubation period: 14-25 d
- infectivity period: 7 d pre-parotitis to 5 d post-parotitis
- upper respiratory tract → lymph nodes → salivary glands, gonads, pancreas, meninges, kidney, heart, thyroid

### History
- non-specific prodome of fever, headache, malaise, myalgias (especially neck pain)
- usually followed within 48 h by parotid swelling secondary to parotitis (bilateral, preauricular, ear pushed up and out)
- parotid gland is tender and pain worsened with spicy or sour foods
- one third of infections do not cause clinically apparent salivary gland swelling and may simply present as an URTI

### Investigations
- clinical diagnosis, but may be confirmed with IgM positive serology within 4 wk of acute infection
  - may also use PCR or viral cultures from oral secretions, urine, blood, and CSF
  - blood work: CBC (leukopenia with relative lymphocytosis), serum amylase (elevated)

### Management
- mainly supportive: analgesics, antipyretics, warm or cold packs to parotid may be soothing
- admit to hospital if serious complications (meningitis, pancreatitis)
- droplet precautions recommended until 5 d after onset of parotid swelling
- prophylaxis: routine vaccination (see *Routine Immunization*, P3)

### Complications
- common: aseptic meningitis, orchitis/oophoritis
- less common: encephalitis, pancreatitis, thyroiditis, myocarditis, arthritis, GN, ocular complications, hearing impairment
Pertussis

Definition
• prolonged respiratory illness characterized by paroxysmal coughing and inspiratory “whoop”

Epidemiology
• ~10 million children <1 yr old affected worldwide, causes up to 400,000 deaths/yr
• greatest incidence among children <1 yr (not fully immunized) and adolescents (waning immunity)

Etiology
• *Bordetella pertussis*: Gram negative pleomorphic rod
• highly contagious; transmitted via respiratory droplets released during intense coughing
• incubation period: 6-20 d; most contagious during catarrhal phase but may remain contagious for weeks after

History
• prodromal catarrhal stage
  • lasts 1-7 d; URTI symptoms (coryza, mild cough, sneezing) with NO or LOW-GRADE fever
• paroxysmal stage
  • lasts 4-6 wk; characterized by paroxysms of cough (“100 day cough”), sometimes followed by inspiratory whoop (“whooping cough”)
  • infants <6 mo may present with post-tussive apnea, whoop is often absent
  • onset of attacks precipitated by yawning, sneezing, eating, physical exertion
  • ± post-tussive emesis, may become cyanotic before whoop
• convalescent stage:
  • lasts 1-2 wk; characterized by occasional paroxysms of cough, but decreased frequency and severity
  • non-infectious but cough may last up to 6 mo

Investigations
• NP specimen using aspirate or NP swab
  • gold standard: culture using special media (Regan-Lowe agar)
  • PCR to detect pertussis antigens
• blood work: CBC (lymphocytosis) and serology (antibodies against *B. pertussis*)

Management
• admit if paroxysms of cough are associated with cyanosis and/or apnea and give O₂
• supportive care
• antimicrobial therapy indicated if *B. pertussis* isolated, or symptoms present for <21 d
  • use macrolide antibiotics (azithromycin, erythromycin, or clarithromycin)
• droplet isolation until 5 d of treatment and report to Public Health
• prophylaxis
  • macrolide antibiotics for all household contacts
  • prevention with vaccination in infants and children (Pentacel®), and booster in adolescents (Adacel®) (see Routine Immunization, P3)

Complications
• pressure-related from paroxysms: subconjunctival hemorrhage, rectal prolapse, hernias, epistaxis
• respiratory: sinusitis, pneumonia, aspiration, atelectasis, pneumomediastinum, pneumothorax, alveolar rupture
• neurological: seizures (~3%), encephalopathy, ICH
• mortality: ~0.3%; highest risk in infants <6 mo old

Pneumonia
• see Pediatric Respirology, P88

Periorbital (Preseptal) and Orbital Cellulitis
• see Ophthalmology, OP10

Cardinal Signs of Orbital Cellulitis
• Ophthalmoplegia/diplopia
• Decreased visual acuity
• Pain with extraocular eye movement

Sexually Transmitted Infection
• see Family Medicine, FM45 and Gynecology, GY25
Sinusitis

- see Family Medicine, FM46
- complication of ≤10% of URTIs in children
- clinical diagnosis
- diagnostic imaging is NOT required to confirm diagnosis in children
  - routine CT not recommended, but consider if suspect complications of sinusitis, persistent/recurrent disease, need for surgery
- antibiotic therapy for all children (although nearly half resolve spontaneously within 4 wk)
- complications: preseptal/orbital (preseptal/orbital cellulitis, orbital abscess, osteomyelitis, etc.), intracranial (meningitis, abscess, etc.), Pott's Puffy tumour

Urinary Tract Infection

Definition
- infection of the urinary bladder (cystitis) and/or kidneys (pyelonephritis)

Epidemiology
- overall prevalence in infants and young children presenting with fever is 7%
- <4-6 wk old: more common in boys
- >1 yr old: females have two- to four-fold higher prevalence

Etiology
- majority (>95%) have a monomicrobial cause (~70% E. coli)
- Gram-negative bacilli: E. coli, Klebsiella, Proteus, Enterobacter, Pseudomonas
- Gram-positive cocci: S. saprophyticus, Enterococcus

Risk Factors
- non-modifiable: female gender, Caucasian, previous UTIs, family history
- modifiable: urinary tract abnormalities (VUR, neurogenic bladder, obstructive uropathy, posterior urethral valve), dysfunctional voiding, repeated bladder catheterization, uncircumcised males, labial adhesions, sexually active, constipation, toilet training

History
- infants and young child: often just fever or non-specific symptoms (poor feeding, irritability, FTT, jaundice if <28 d old, vomiting)
- older child: fever, urinary symptoms (dysuria, urgency, frequency, incontinence, hematuria), abdominal and/or flank pain

Physical Exam
- infants and young child: toxic vs non-toxic, febrile, FTT, jaundice; look for external genitalia abnormalities (phimosis, labial adhesions) and lower back signs of occult myelodysplasia (e.g. hair tufts), which may be associated with neurogenic bladder
- older child: febrile, suprapubic and/or CVA tenderness, abdominal mass (enlarged bladder or kidney); may present with short stature, FTT, or HTN secondary to renal scarring from previously unrecognized or recurrent UTIs

Investigations
- sterile urine specimen
  - clean catch, catheterization, or suprapubic aspiration
  - urinalysis (leukocyte esterase, nitrites, erythrocytes, hemoglobin), microscopy (bacteria and leukocytes, erythrocytes), C&S
  - diagnosis established if urinalysis suggests infection AND if ≥50,000 colony-forming units per mL of a uropathogen cultured

Management
- admit if: <2 mo old, urosepsis, persistent vomiting, inability to tolerate oral medication, moderate-severe dehydration, immunocompromised, complex urologic pathology, inadequate follow-up, failure to respond to outpatient therapy
- supportive care: maintenance of hydration and adequate pain control
- antibiotics
  - base on local antimicrobial susceptibility patterns
  - commence broad empiric therapy until results of urine C&S known, and then tailor as appropriate
  - neonates: IV ampicillin and gentamicin
  - infants and older children: oral antibiotics (based on local E.coli sensitivity) if outpatient; IV ampicillin and gentamicin if inpatient
  - duration 7-10 d
- imaging
  - renal and bladder U/S for all febrile infants (<2 yr) with UTIs looking for anatomical abnormalities, hydrenephrosis, abscess
  - VCUG not recommended after 1st febrile UTI unless U/S reveals hydrenephrosis, obstructive uropathies or other signs suggestive of high-grade VUR

Features Suggestive of Pyelonephritis
- High-grade fever
- Flank or high abdominal pain
- CVA tenderness on palpation

Bagged urine specimen not useful for ruling in UTI (high false positive rate >85%), but useful for ruling out UTI (high sensitivity)

Prophylaxis After First Febrile Urinary Tract Infection in Children? A Multicentre, Randomized Controlled, Noninferiority Trial

Study: Randomized, controlled, open-label, 2 armed, noninferiority trial.

Patients: 338 patients aged 2 mo to <7 yr who had a first episode of febrile UTI.

Intervention: No prophylaxis vs. prophylaxis.

Outcome: Recurrence rate of febrile UTI and rate of renal scarring.

Results: No significant difference in recurrence rate or in the rate of renal scarring between the prophylaxis and no prophylaxis group.
• follow-up: outpatients to return in 24-48 h if no clinical response and seek prompt medical evaluation for future febrile illnesses
• prophylaxis: generally not recommended unless higher grades of VUR

**Complications**

• long-term morbidity: focal renal scarring develops in 8% of patients; long-term significance unknown

---

**Neonatology**

**Gestational Age and Size**

**Definitions**

• classification by GA
  - preterm: <37 wk
  - near-term: 35-37 wk
  - term: 37-42 wk
  - post-term: >42 wk

• classification by birth weight
  - SGA: 2 SD < mean weight for GA or <10th percentile
  - AGA: within 2 SD of mean weight for GA
  - LGA: 2 SD > mean weight for GA or >90th percentile

**Table 26. Abnormalities of Gestational Age and Size**

<table>
<thead>
<tr>
<th>Features</th>
<th>Causes</th>
<th>Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Term Infants</td>
<td>Spontaneous: cause unknown</td>
<td>RDS, apnea of prematurity, chronic lung disease, bronchopulmonary dysplasia</td>
</tr>
<tr>
<td>&lt;37 wk</td>
<td>Maternal disease: HTN, DM, cardiac and renal disorders</td>
<td>Feeding difficulties, NEC</td>
</tr>
<tr>
<td></td>
<td>Fetal conditions: multiple pregnancy,</td>
<td>Hypocalcemia, hypoglycemia, hypothermia</td>
</tr>
<tr>
<td></td>
<td>congenital abnormalities</td>
<td>Anemia, jaundice</td>
</tr>
<tr>
<td></td>
<td>Pregnancy issues: placental insufficiency,</td>
<td>Retinopathy of prematurity</td>
</tr>
<tr>
<td></td>
<td>placenta previa, uterine malformations,</td>
<td>ICH/VH</td>
</tr>
<tr>
<td></td>
<td>previous preterm birth, infection</td>
<td>PDA</td>
</tr>
<tr>
<td></td>
<td>Behavioural and psychological contributors: smoking, EtOH, drug use, psychosocial stressors</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sociodemographic factors: age, socioeconomic conditions</td>
<td></td>
</tr>
<tr>
<td>Post-Term Infants</td>
<td>Most cases unknown</td>
<td>Increased risk of stillbirth or neonatal death</td>
</tr>
<tr>
<td>&gt;42 wk</td>
<td>Increased in first pregnancies</td>
<td>Fetal “postmaturity syndrome”: impaired growth due to placental dysfunction</td>
</tr>
<tr>
<td>Leathery skin</td>
<td>Previous post-term birth</td>
<td>Meconium aspiration</td>
</tr>
<tr>
<td>Meconium staining</td>
<td>Genetic factors</td>
<td></td>
</tr>
<tr>
<td>SGA Infants</td>
<td>Extrinsic causes: placental insufficiency, poor nutrition, HTN, multiple pregnancies, drugs, EtOH, smoking</td>
<td>Perinatal hypoxia</td>
</tr>
<tr>
<td>&lt;10th percentile</td>
<td></td>
<td>Hypoglycemia, hypocalcemia, hypothermia</td>
</tr>
<tr>
<td>Asymmetric (head-sparing): late onset, growth arrest</td>
<td>Hyperviscosity (polycythemia), jaundice, hypomotility</td>
<td></td>
</tr>
<tr>
<td>Symmetric: early onset, lower growth</td>
<td>Intrinsic causes: maternal infections (TORCH), congenital abnormalities, syndromal, idiopathic</td>
<td>PDA</td>
</tr>
<tr>
<td>LGA Infants</td>
<td>Maternal DM</td>
<td>Birth trauma, perinatal depression (meconium aspiration)</td>
</tr>
<tr>
<td>&gt;90th percentile</td>
<td>Racial or familial factors</td>
<td>RDS, TTN</td>
</tr>
<tr>
<td></td>
<td>Increasing parity</td>
<td>Jaundice, polycythemia</td>
</tr>
<tr>
<td></td>
<td>Previous LGA infant, high BMI, large pregnancy weight gain</td>
<td>Hypoglycemia, hypocalcemia</td>
</tr>
<tr>
<td></td>
<td>Certain syndromes</td>
<td></td>
</tr>
</tbody>
</table>

**Routine Neonatal Care**

1. erythromycin ointment: applied to both eyes for prophylaxis of ophthalmia neonatorum (of questionable efficacy)
2. vitamin K IM: prophylaxis against HDNB
3. newborn screening tests in Ontario
   - in Ontario, newborn screening tests for
     - metabolic disorders (amino acid disorders, organic acid disorders, fatty acid oxidation defects, biotinidase deficiency, galactosemia)
     - blood disorders (SCD, other hemoglobinopathies)
     - endocrine disorders (CAH, congenital hypothyroidism)
     - others (CF, severe combined immunodeficiency)
     - congenital hearing loss
4. if mother Rh negative: send cord blood for blood group and direct antiglobulin test
5. if mother hepatitis B surface antigen positive: HBIG and start hepatitis B vaccine series
**Neonatal Resuscitation**

- assess Apgar score at 1 and 5 min
- if <7 at 5 min then reassess q5min, until >7
- do not wait to assign Apgar score before initiating resuscitation

### Table 27. Apgar Score

<table>
<thead>
<tr>
<th>Sign</th>
<th>0</th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart Rate</td>
<td>Absent</td>
<td>&lt;100/min</td>
<td>&gt;100/min</td>
</tr>
<tr>
<td>Respiratory Effort</td>
<td>Absent</td>
<td>Slow, irregular</td>
<td>Good, crying</td>
</tr>
<tr>
<td>Irritability</td>
<td>No response</td>
<td>Grimace</td>
<td>Cough/cry</td>
</tr>
<tr>
<td>Tone</td>
<td>Limp</td>
<td>Some flexion of extremities</td>
<td>Active motion</td>
</tr>
<tr>
<td>Colour</td>
<td>Blue, pale</td>
<td>Body pink, extremities blue (acrocyanosis)</td>
<td>Completely pink</td>
</tr>
</tbody>
</table>

### Initial Resuscitation

- anticipation: know maternal history, history of pregnancy, labour, and delivery
- steps to take for all infants (before ABCs)
  - warm (radiant heater, warm towels) and dry the newborn (remove wet towels)
  - position and clear airway (“sniffing” position)
  - stimulate infant: rub lower back gently or flick soles of feet EXCEPT if meconium present (in which case tracheal suction first)
  - assess breathing and heart rate

- Airway
  - if meconium is present and
    - baby is vigorous (strong respiratory effort, good muscle tone, HR >100): no further resuscitative interventions required
    - baby is not vigorous: intubate and suction trachea while monitoring vital signs; if prolonged or unsuccessful intubation, attempt bag mask ventilation
  - if no meconium and suction required, suction mouth first and then nose

- Breathing
  - if HR <100 or apneic, apply PPV
  - PPV at rate of 40-60/min with enough pressure to see visible chest expansion and note increase in HR
  - monitor preductal SpO₂
  - if PPV not effective (no increase in HR, no chest rise, low SpO₂), incorporate corrective actions

- Circulation
  - if HR <60 after 30 s of effective ventilation, start chest compressions (“60 or less, compress”)
  - should provide 100% oxygen as soon as chest compressions are required
  - chest compressions at lower 1/3 of the sternum and 1/3 of the AP depth at a rate of 120 events per min (3 compressions:1 ventilation = 120 compressions/min:40 breaths/min)

### Table 28. Interventions Used in Neonatal Resuscitation

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Schedule</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine (adrenaline)</td>
<td>0.1-0.3 mL/kg/dose of 1:10,000 (0.01-0.03 mg/kg) IV 0.5-1 mL/kg/dose of 1:10,000 (0.05-0.1 mg/kg) endotracheally can be considered while awaiting IV access (IV preferred) Can be repeated q3-5 min prn</td>
<td>HR &lt;60 and not rising</td>
<td>Side effects: tachycardia, HTN, cardiac arrhythmias</td>
</tr>
<tr>
<td>Naloxone (Narcan®)</td>
<td>0.1 mg/kg IV/IM</td>
<td>Not recommended as part of initial resuscitation HR and oxygenation should be restored by supporting ventilation</td>
<td>Do not use for chronic opiate exposure – may cause withdrawal symptoms including HTN, irritability, seizures Action of opioid outlasts action of naloxone therefore close monitoring required after administration</td>
</tr>
<tr>
<td>Fluid Bolus (NS, whole blood, Ringer’s lactate)</td>
<td>10 mL/kg</td>
<td>May need to be repeated Avoid giving too rapidly as large volume rapid infusions can be associated with IVH</td>
<td>Evidence of hypovolemia</td>
</tr>
</tbody>
</table>
### Approach to the Depressed Newborn

- A depressed newborn lacks one or more of the following characteristics of a normal newborn:
  - Pulse > 100 bpm
  - Cries when stimulated
  - Actively moves all extremities
  - Has a good strong cry
- Approximately 10% of newborn babies require assistance with breathing after delivery.

#### Table 29. Etiology of Respiratory Depression in the Newborn

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Problems</td>
<td>RDS/hyaline membrane disease, Pulmonary hypoplasia, CNS depression, MAS,\</td>
</tr>
<tr>
<td></td>
<td>Pneumonia, Pneumothorax, Pleural effusions, Congenital malformations</td>
</tr>
<tr>
<td>Anemia (severe)</td>
<td>Erythroblastosis fetalis, Secondary hydrops fetalis</td>
</tr>
<tr>
<td>Maternal Causes</td>
<td>Drugs/anesthesia (opiates, magnesium sulphate), DM, Maternal myasthenia</td>
</tr>
<tr>
<td></td>
<td>gravis</td>
</tr>
<tr>
<td>Congenital Malformations/Birth Injury</td>
<td>Nuchal cord, perinatal depression, Bilateral phrenic nerve injury, Potter’s sequence</td>
</tr>
<tr>
<td>Shock</td>
<td>Antepartum hemorrhage</td>
</tr>
<tr>
<td>CHD</td>
<td>Transpation of the great arteries with intact ventricular septum</td>
</tr>
<tr>
<td>Other</td>
<td>Hypothermia, Hypoglycemia, Infection</td>
</tr>
</tbody>
</table>

### Diagnosis

- Vital signs
- Detailed maternal history: include prenatal care, illnesses, use of drugs, labour, previous high risk pregnancies, infections during pregnancy, current infections, duration of ruptured membranes, blood type and Rh status, amniotic fluid status, GA, meconium, Apgar scores
- Clinical findings (observe for signs of respiratory distress such as cyanosis, tachypnea, retractions, grunting, temperature instability)
- Laboratory results (CBC, ABG, blood type, glucose)
- Transillumination of chest to evaluate for pneumothorax
- CXR

### Management

- ABCs
- Intubation and suction if meconium present
- Apply tactile stimulation if no meconium
- Provide PPV if apneic or HR < 100 bpm
- Monitor SpO2 and HR (if < 60 bpm, start chest compressions)
- Provide ventilatory support and treat the underlying cause

## Common Conditions of Neonates

### Apnea

#### Definition

- "Periodic breathing": normal respiratory pattern seen in newborns in which periods of rapid respiration are alternated with pauses lasting 5-10 s
- "Apnea": absence of respiratory gas flow for > 20 s (or less if associated with bradycardia or desaturation) – 3 types
  - Central: no chest wall movement, no signs of obstruction
  - Obstructive: chest wall movement continues against obstructed upper airway, no airflow
  - Mixed: combination of central and obstructive apnea

#### Differential Diagnosis

- In term infants, apnea requires full workup as it can be associated with sepsis
Common Conditions of Neonates

• other causes
  ▪ CNS
    ▪ apnea of prematurity (<34 wk): combination of CNS immaturity and obstructive apnea; resolves by 36 wk GA; diagnosis of exclusion
    ▪ seizures
    ▪ ICH
    ▪ hypoxic injury
  ▪ infectious: sepsis, meningitis, NEC
  ▪ GI: GERD, aspiration with feeding
  ▪ metabolic: hypoglycemia, hyponatremia, hypocalcemia, inborn error of metabolism
  ▪ cardiovascular: anemia, hypovolemia, PDA, heart failure
  ▪ medications: morphine

Management
• O₂, ventilatory support, maintain normal blood gases
• tactile stimulation
• correct underlying cause
• medications: methylxanthines (caffeine) stimulate the CNS and diaphragm and are used for apnea of prematurity (not in term infants)

Bleeding Disorders in Neonates

Clinical Presentation
• oozing from the umbilical stump, excessive bleeding from peripheral venipuncture/heel stick sites/IV sites, large caput succedaneum, cephalohematomas (in absence of significant birth trauma), subgaleal hemorrhage and prolonged bleeding following circumcision

Etiology
• 4 major categories
  ▪ increased platelet destruction: maternal ITP or SLE, infection/sepsis, DIC, neonatal alloimmune thrombocytopenia, autoimmune thrombocytopenia
  ▪ decreased platelet production/function: pancytopenia, bone marrow replacement, Fanconi anemia, Trisomy 13 and 18
  ▪ metabolic: congenital thyrotoxicosis, inborn error of metabolism
  ▪ coagulation factor deficiencies (see Hematology, H31): hemophilia A/B, HDNB

NEONATAL ALLOIMMUNE THROMBOCYTOPENIA

Epidemiology
• 1 per 4,000-5,000 live births

Pathophysiology
• platelet equivalent of Rh disease of the newborn
• occurs when mother is negative for HPA and fetus is positive
• development of maternal IgG antibodies against HPA antigens on fetal platelets

Clinical Presentation
• petechiae, purpura, thrombocytopenia in otherwise healthy neonate
• severe disease can lead to intracranial bleeding

Diagnosis
• maternal and paternal platelet typing and identification of platelet alloantibodies

Treatment
• IVIg to mother prenatally starts in second trimester ± steroids ± fetal platelet transfusions
• treat neonate with IVIg
• if transfusion required should be with washed maternal platelets or donor HPA negative platelets

AUTOIMMUNE THROMBOCYTOPENIA

Pathophysiology
• caused by antiplatelet antibodies from maternal ITP or SLE
• passive transfer of antibodies across placenta

Clinical Presentation
• similar presentation to neonatal alloimmune thrombocytopenia, but thrombocytopenia usually less severe

Treatment
• steroids to mother for 10-14 d prior to delivery or IVIg to mother before delivery
• treat neonate with IVIg (usually if platelets <60,000)
• transfusion of infant with maternal/donor platelets only in severe cases, as antibodies will destroy transfused platelets
HEMORRHAGIC DISEASE OF THE NEWBORN

Pathophysiology
- caused by vitamin K deficiency
- factors II, VII, IX, X are vitamin K-dependent, therefore both PT and PTT are abnormal

Etiology and Clinical Presentation
- neonates at risk of vitamin K deficiency if: vitamin K poorly transferred across the placenta; maternal use of antiepileptics; insufficient bacterial colonization of colon at birth to synthesize vitamin K; breastfed (vitamin K intake inadequate in breastfed infants)
- neonate may present with hematomas, ICH (causing apnea or seizures), internal bleeding, hematuria, bruising, prolonged bleeding (often from mucous membranes, umbilicus, circumcision, and venipunctures)

Prevention
- vitamin K IM administration at birth to all newborns

Bronchopulmonary Dysplasia

Definition
- also known as chronic lung disease
- clinically defined as $O_2$ requirement for >28 d plus persistent need for oxygen and/or ventilatory support at 36 wk corrected GA
- damage to developing lungs with prolonged intubation/ventilation

Investigations
- CXR findings may demonstrate decreased lung volumes, areas of atelectasis, and hyperinflation

Treatment
- no good treatments
- gradual wean from ventilator, optimize nutrition
- dexamethasone may help decrease inflammation and encourage weaning, but use of dexamethasone is associated with increased risk of adverse neurodevelopmental outcomes

Prognosis
- chronic respiratory failure may lead to pulmonary HTN, poor growth, and right-sided heart failure
- patients with bronchopulmonary dysplasia may continue to have significant impairment and deterioration in lung function late into adolescence
- some lung abnormalities may persist into adulthood including airway obstruction, airway hyper-reactivity, and emphysema
- associated with increased risk of adverse neurodevelopmental outcomes

Figure 12. Approach to neonatal cyanosis
Management

• ABGs
  - elevated CO₂ suggests respiratory cause
  - hyperoxia test (to distinguish between cardiac and respiratory causes of cyanosis): get baseline PaO₂ in room air, then PaO₂ on 100% O₂ for 10-15 min
    - PaO₂ <150 mmHg: suggests cyanotic CHD or possible PPHN (see Pediatric Cardiology, P16)
    - PaO₂ >150 mmHg: suggests cyanosis likely due to respiratory or non-cardiac cause
  - CXR: look for respiratory abnormalities (respiratory tract malformations, evidence of shunting, pulmonary infiltrates) and cardiac abnormalities (cardiomegaly, abnormalities of the great vessels)

Diaphragmatic Hernia

• see General Surgery, GS64

Definition

• developmental defect of the diaphragm with herniation of abdominal organs into thorax
• associated with pulmonary hypoplasia and PPHN

Clinical Presentation

• respiratory distress, cyanosis
• scaphoid abdomen and barrel-shaped chest
• affected side dull to percussion and breath sounds absent, may hear bowel sounds instead
• heart sounds shifted to contralateral side
• asymmetric chest movements, trachea deviated away from affected side
• may present outside of neonatal period
• often associated with other anomalies (cardiovascular, CNS, chromosomal abnormalities)
• CXR: bowel loops in thorax (usually left side), displaced mediastinum

Treatment

• immediate intubation required at birth: DO NOT bag mask ventilate because air will enter stomach and further compress lungs
• place large bore orogastric tube to decompress bowel
• initial stabilization and management of pulmonary hypoplasia and PPHN, hemodynamic support and surgery when stable

Hypoglycemia

Definition

• glucose <2.6 mmol/L

Etiology

• decreased carbohydrate stores: premature, SGA, RDS, maternal HTN
• endocrine: hormonal deficiencies (GH, cortisol, epinephrine), insulin excess (infant of diabetic mother, Beckwith-Wiedemann syndrome/islet cell hyperplasia), HPA axis suppression (panhypopituitarism)
• inborn errors of metabolism: fatty acid oxidation defects, galactosemia
• miscellaneous: sepsis, hypothermia, polycythemia

Clinical Findings

• signs often non-specific and subtle: lethargy, poor feeding, irritability, tremors, apnea, cyanosis, seizures

Management

• identify and monitor infants at risk (pre-feed blood glucose checks)
• begin oral feeds as soon as possible after birth and ensure regular feeds
• if significant and/or symptomatic hypoglycemia, provide glucose IV and titrate according to blood sugar levels
• if persistent hypoglycemia or no predisposing cause, send “critical blood work” during an episode of hypoglycemia: ABG, ammonia, β-hydroxybutyrate, cortisol, free fatty acids, GH, insulin, lactate, urine dipstick for ketones

Carboxyhemoglobinemia (secondary to carbon monoxide poisoning) results in impaired binding of oxygen to hemoglobin but does not discolour the blood. Therefore it may not register on pulse oximetry and cyanosis may not be evident clinically.

Methemoglobinemia typically reads higher on pulse oximetry than the true level of oxyhemoglobin. Methemoglobin alters the absorption of red light at the two wavelengths that pulse oximetry uses to predict oxygen saturation.
**Intraventricular Hemorrhage**

**Definition**
- hemorrhage originating in the periventricular subependymal germinal matrix

**Epidemiology**
- incidence and severity inversely proportional to GA
- 50% of IVH occurs within 8 h of birth; 90% occurs by day 3

**Risk Factors**
- prematurity (<32 wk), BW <1,500 g, need for vigorous resuscitation at birth, pneumothorax, ventilated preterm infants, hemodynamic instability, RDS, coagulopathy

**Clinical Presentation**
- many infants with IVH are asymptomatic
- subtle signs: apnea, bradycardia, changes in tone or activity, altered LOC
- catastrophic presentation: bulging fontanelle, sudden drop in hematocrit, acidosis, seizures, hypotension

**Classification**
- Papile classification
- parenchymal hemorrhage may also occur in the absence of IVH
- routine head U/S screening of all preterm infants <32 wk or <1,500 g gestation throughout NICU stay
- consider MRI at term for extremely LBW infants

**Management of Acute Hemorrhage**
- supportive care to maintain blood volume and acid-base status
- avoid fluctuations in blood pressure and cerebral blood flow
- follow-up with serial imaging

**Prognosis**
- outcome depends on grade of IVH
- short-term sequelae for severe IVH: mortality, extension of bleed, posthemorrhagic hydrocephalus, posthemorrhagic infarction, cyst formation
- possible long-term major neurological sequelae: CP, cognitive deficits, motor deficits, visual and hearing impairment
- Grades I and II hemorrhages have a relatively favourable prognosis
- greatest morbidity and mortality is seen with Grade IV hemorrhage and posthemorrhagic hydrocephalus requiring ventriculoperitoneal shunt placement

**Jaundice**

**Clinical Presentation**
- jaundice is visible at serum bilirubin levels of 85-120 µmol/L; visual assessment is often misleading
- look at sclera, tip of nose in natural light
- jaundice more severe/prolonged (due to increased retention of bilirubin in the circulation) with: prematurity, acidosis, hypoalbuminemia, dehydration, hemolysis

**Hyperbilirubinemia**

- **Unconjugated**
  - **Pathologic**
    - Intrinsic
      - Membrane
        - Spherocytosis
      - Enzyme
        - G6PD deficiency
      - PK deficiency
      - Hemoglobin
        - α-thalassemia
    - Extrinsic
      - Immune
        - ABO incompatibility
      - Rh incompatibility
      - Kell, Duffy, etc.
      - Non-immune
        - Spleenomegaly
      - Seizis
        - AV malformation
  - **Physiologic**
    - Non-Hemolytic
      - Hematoma
        - cephalohematoma
      - Polycythemia
      - Sepsis
      - Hypothyroidism
      - Gilbert syndrome
      - Crigler-Najjar
  - **Always pathologic**
    - Hepatic
      - Infectious
        - Sepsis
      - Hep B, TORCH
    - Metabolic
      - Galactosemia
      - Tyrosinemia
      - α-1-antitrypsin deficiency
      - Hypothyroidism
    - CF
    - Drugs
    - TPN
    - Idiopathic neonatal hepatitis

**Figure 13. Approach to neonatal hyperbilirubinemia**
PHYSIOLOGIC JAUNDICE

Epidemiology
• term infants: onset 3-4 d of life, resolution by 10 d of life
• premature infants: higher peak and longer duration

Pathophysiology
• increased hematocrit and decreased RBC lifespan
• immature glucuronyl transferase enzyme system (slow conjugation of bilirubin)
• increased enterohepatic circulation

Breastfeeding Jaundice
• common; due to a lack of milk production → dehydration → exaggerated physiologic jaundice

Breast Milk Jaundice
• 1 per 200 breastfed infants
• glucuronyl transferase inhibitor found in breast milk
• onset 7 d of life, peak at 2-3 wk of life, usually resolved by 6 wk

Table 30. Risk Factors for Jaundice

<table>
<thead>
<tr>
<th>Maternal Factors</th>
<th>Perinatal Factors</th>
<th>Neonatal Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethnic group (e.g. Asian, native American)</td>
<td>Birth trauma (cephalohematoma, ecchymoses)</td>
<td>Difficulty establishing breastfeeding</td>
</tr>
<tr>
<td>Complications during pregnancy (infant of diabetic mother, Rh or ABO incompatibility)</td>
<td>Prematurity</td>
<td></td>
</tr>
<tr>
<td>Breastfeeding</td>
<td></td>
<td>Genetic factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Polycythemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drugs</td>
</tr>
</tbody>
</table>

Table 31. Causes of Neonatal Jaundice by Age

<table>
<thead>
<tr>
<th>&lt;24 h</th>
<th>24-72 h</th>
<th>72-96 h</th>
<th>Prolonged (&gt;1 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALWAYS PATHOLOGIC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemolytic</td>
<td>Physiologic, polycythemia</td>
<td>Physiologic ± breastfeeding</td>
<td>Breast milk jaundice</td>
</tr>
<tr>
<td>Rh or ABO incompatibility</td>
<td>Dehydration</td>
<td>Sepsis</td>
<td>Prolonged physiologic</td>
</tr>
<tr>
<td>Sepsis</td>
<td>(breastfeeding jaundice)</td>
<td></td>
<td>jaundice in preterm</td>
</tr>
<tr>
<td>Congenital infection (TORCH)</td>
<td>Hemolysis</td>
<td></td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Severe bruising/hemorrhage</td>
<td>G6PD deficiency</td>
<td></td>
<td>Neonatal hepatitis</td>
</tr>
<tr>
<td></td>
<td>Pyruvate kinase deficiency</td>
<td></td>
<td>Conjugation dysfunction</td>
</tr>
<tr>
<td></td>
<td>Spherocytosis</td>
<td>e.g. Gilbert syndrome,</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bruising, hemorrhage,</td>
<td>Crigler-Najjar syndrome</td>
<td></td>
</tr>
<tr>
<td></td>
<td>hematomata</td>
<td>Inborn errors of metabolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sepsis/congenital infection</td>
<td>e.g. galactosemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biliary tract obstruction</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>e.g. biliary atresia</td>
<td></td>
</tr>
</tbody>
</table>

PATHOLOGIC JAUNDICE
• all cases of conjugated hyperbilirubinemia; some cases of unconjugated hyperbilirubinemia are pathologic

Investigations
• unconjugated hyperbilirubinemia
  ▪ hemolytic workup: CBC, reticulocyte count, blood group (mother and infant), peripheral
    blood smear, Coombs test
  ▪ if baby is unwell or has fever: septic workup (CBC and differential, blood and urine cultures
    ± LP, CXR)
  ▪ other: G6PD screen (especially in males), TSH
• conjugated hyperbilirubinemia must be investigated without delay
  ▪ consider liver enzymes (AST, ALT), coagulation studies (PT, PTT), serum albumin, ammonia, TSH, TORCH screen, septic workup, galactosemia screen (erythrocyte galactose-1-phosphate uridyltransferase levels), metabolic screen, abdominal U/S, HIDA scan, sweat
  chloride

TREATMENT OF UNCONJUGATED HYPERBILIRUBINEMIA
• to prevent kernicterus
• breastfeeding does not usually need to be discontinued, ensure adequate feeds and hydration
• lactation consultant support, mother to pump after feeds
• treat underlying causes (e.g. sepsis)
• phototherapy (blue-green wavelength, not UV light)
  ▪ insoluble unconjugated bilirubin is converted to excretable form via photoisomerization
  ▪ serum bilirubin should be monitored during and immediately after therapy (risk of rebound
    because photoisomerization reversible when phototherapy discontinued)
- contraindicated in conjugated hyperbilirubinemia: results in “bronzed” baby
- side effects: skin rash, diarrhea, eye damage (eye shield used routinely for prevention), dehydration
- use published guidelines and nomogram for initiation of phototherapy
- exchange transfusion
  - indications: high bilirubin levels as per published graphs based on age, weeks gestation
  - most commonly performed for hemolytic disease and G6PD deficiency
  - use of IVIg in case of severe hyperbilirubinemia (DAT+) becoming evidence-based practice

KERNICTERUS

Etiology
- unconjugated bilirubin concentrations exceed albumin binding capacity and bilirubin is deposited in the brain resulting in permanent damage (typically basal ganglia or brainstem)
- incidence increases as serum bilirubin levels increase above 340 µmol/L
- can occur at lower levels in presence of sepsis, meningitis, hemolysis, hypoxia, acidosis, hypothermia, hypoglycemia, and prematurity

Clinical Presentation
- up to 15% of infants have no obvious neurologic symptoms
- early stage: lethargy, hypotonia, poor feeding, emesis (bilirubin encephalopathy)
- mid stage: hypertonia, high pitched cry, opisthotonic posturing (back arching), bulging fontanelle, seizures, pulmonary hemorrhage
- late stage (first year and beyond)
  - hypotonia, delayed motor skills, extrapyramidal abnormalities (choreoathetoid CP), gaze palsy, mitral regurgitation, sensorineural hearing loss

Prevention
- exchange transfusion, IVIg if indicated

BILIARY ATRESIA

Definition
- atresia of the extrahepatic bile ducts which leads to cholestasis and increased conjugated bilirubin after the first week of life
- progressive obliterative cholangiopathy

Epidemiology
- incidence: 1:10,000-15,000 live births
- associated anomalies in 10-35% of cases: situs inversus, congenital heart defects, polysplenia

Clinical Presentation
- dark urine, pale stool, jaundice (persisting for >2 wk), abdominal distension, hepatomegaly

Diagnosis
- conjugated hyperbilirubinemia, abdominal U/S
- HIDA scan (may be bypassed in favour of biopsy if timing of diagnosis is critical)
- liver biopsy

Treatment
- surgical drainage procedure
- hepatopancreatobiliary (Kasai procedure; most successful if <8 wk of age)
- two-thirds will eventually require liver transplantation
- vitamins A, D, E, and K; diet should be enriched with medium-chain triglycerides to ensure adequate fat ingestion

Necrotizing Enterocolitis

Definition
- intestinal inflammation associated with focal or diffuse ulceration and necrosis
- primarily affecting terminal ileum and colon

Epidemiology
- affects 1-5% of preterm newborns admitted to NICU
Pathophysiology
- postulated mechanism of bowel ischemia: mucosal damage and enteral feeding → bacterial growth → bowel necrosis/gangrene/perforation

Risk Factors
- prematurity (immature defenses)
- asphyxia, shock (poor bowel perfusion)
- hyperosmolar feeds
- enteral feeding with formula (breast milk can be protective)
- sepsis

Clinical Presentation
- usually presents at 2-3 wk of age
- distended abdomen
- increased amount of gastric aspirate/vomitus with bile staining
- frank or occult blood in stool
- feeding intolerance
- diminished bowel sounds
- signs of bowel perforation (sepsis, shock, peritonitis, DIC)

Investigations
- AXR: pneumonitis intestinalis (intramural air is a hallmark of NEC), free air, fixed loops, ileus, thickened bowel wall, portal venous gas
- CBC, ABG, lactate, blood culture, electrolytes
- high or low WBC, low platelets, hyponatremia, acidosis, hypoxia, hypercapnea

Treatment
- NPO (7-10 d), vigorous IV fluid resuscitation, decompression with NG tube, supportive therapy
- TPN
- antibiotics (usually ampicillin, gentamicin ± metronidazole if risk of perforation x 7-10 d)
- serial AXRs detect early perforation (40% mortality in perforated NEC)
- peritoneal drain/surgery if perforation
- surgical resection of necrotic bowel and surgery for complications (e.g. perforation, strictures)

Persistent Pulmonary Hypertension of the Newborn

Epidemiology
- incidence 1.9/1,000 live births

Clinical Presentation
- usually presents within 12 h of birth with severe hypoxemia/cyanosis; may have only mild respiratory distress

Pathophysiology
- persistence of fetal circulation as a result of persistent elevation of pulmonary vascular resistance
- R → L shunt through PDA, foramen ovale → decreased pulmonary blood flow and hypoxemia → further pulmonary vasoconstriction

Risk Factors
- secondary PPHN: asphyxia, MAS, RDS, sepsis, pneumonia, structural abnormalities (e.g. diaphragmatic hernia, pulmonary hypoplasia)
- primary PPHN occurs in absence of risk factors
- more common in term or post-term infants

Investigations
- measure pre- and post-ductal oxygen levels
- hyperoxia test to exclude CHD
- ECG (RV strain)
- Echo reveals increased pulmonary arterial pressure and a R → L shunt across PDA and patent foramen ovale; also used to rule out other cardiac defects

Treatment
- maintain good oxygenation (SaO₂ >95%) in at-risk infants
- O₂, given early and tapered slowly, minimize stress and metabolic demands, maintain normal blood gases, circulatory support
- mechanical ventilation, high frequency oscillation in a sedated muscle-relaxed infant
- nitric oxide, surfactant
- extracorporeal membrane oxygenation used in some centres when other therapy fails
Respiratory Distress in the Newborn

Clinical Presentation
- tachypnea: RR >60/min; tachycardia: HR >160/min
- grunting, substernal/intercostal indrawing, nasal flaring
- duskiness, central cyanosis
- decreased air entry, crackles on auscultation

Differential Diagnosis of Respiratory Distress
- pulmonary: RDS, TTN, MAS, pleural effusion, pneumothorax, congenital lung malformations
- infectious: sepsis, pneumonia
- cardiac: CHD (cyanotic, acyanotic), PPHN
- hematologic: blood loss, polycythemia
- anatomic: TEF, congenital diaphragmatic hernia, mucous or meconium plug, upper airway obstruction (see Otolaryngology, OT44)
- metabolic: hypoglycemia, inborn errors of metabolism
- neurologic: CNS damage (trauma, hemorrhage), drug withdrawal syndromes

Investigations
- CXR, ABG (or venous blood gas from umbilical venous line)
- CBC, blood cultures, blood glucose
- Echo, ECG if indicated

Table 32. Distinguishing Features of RDS, TTN, MAS

<table>
<thead>
<tr>
<th></th>
<th>RDS</th>
<th>TTN</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Surfactant deficiency → poor lung compliance due to high alveolar surface tension → atelectasis → 4 surface area for gas exchange → hypoxia + acidosis → respiratory distress “Hyaline membrane disease”</td>
<td>Delayed resorption of fetal lung fluid → accumulation of fluid in peribronchial lymphatics and vascular spaces → tachypnea “Wet lung syndrome”</td>
<td>Meconium is sterile but causes airway obstruction, chemical inflammation, and surfactant inactivation leading to chemical pneumonitis</td>
</tr>
<tr>
<td><strong>Gestational Age</strong></td>
<td>Preterm</td>
<td>Usually term and late preterm</td>
<td>Term and post-term</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td>Maternal DM</td>
<td>Maternal DM</td>
<td>Meconium-stained amniotic fluid</td>
</tr>
<tr>
<td></td>
<td>Preterm delivery</td>
<td>Maternal asthma</td>
<td>Post-term delivery</td>
</tr>
<tr>
<td></td>
<td>Male sex</td>
<td>Male sex</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LBW</td>
<td>Macrosomia (&gt;4,500 g)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acidosis, sepsis</td>
<td>Elective Cesarean section or short labour</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypothermia</td>
<td>Late preterm delivery</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Second born twin</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Presentation</strong></td>
<td>Respiratory distress within first few hours of life, worsens over next 24-72 h</td>
<td>Tachypnea within the first few hours of life ± retractions, grunting, nasal flaring</td>
<td>Respiratory distress within hours of birth</td>
</tr>
<tr>
<td></td>
<td>Hypoxia</td>
<td>Often NO hypoxia or cyanosis</td>
<td>Small airway obstruction, chemical pneumonitis → tachypnea, barrel chest with audible crackles</td>
</tr>
<tr>
<td></td>
<td>Cyanosis</td>
<td></td>
<td>Hypoxia</td>
</tr>
<tr>
<td><strong>CXR Findings</strong></td>
<td>Homogenous infiltrates</td>
<td>Perihilar infiltrates “Wet silhouette”; fluid in fissures</td>
<td>Hyperinflation</td>
</tr>
<tr>
<td></td>
<td>Air bronchograms</td>
<td></td>
<td>Patchy atelectasis</td>
</tr>
<tr>
<td></td>
<td>Decreased lung volumes</td>
<td></td>
<td>Patchy and coarse infiltrates</td>
</tr>
<tr>
<td></td>
<td>May resemble pneumonia (GBS)</td>
<td></td>
<td>10-20% have pneumothorax</td>
</tr>
<tr>
<td></td>
<td>If severe, “white-out” with no differentiation of cardiac border</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td>Prenatal corticosteroids (e.g. Celestone® 12 mg q24h x 2 doses) if risk of preterm delivery &lt;34 wk</td>
<td>Where possible, avoidance of elective Cesarean delivery, particularly before 38 wk GA</td>
<td>If infant is depressed at birth, intubate and suction below vocal cords</td>
</tr>
<tr>
<td></td>
<td>Monitor lecithin:sphingomyelin (L/S) ratio with amniocentesis, L/S &gt;2:1 indicates lung maturity</td>
<td>Avoidance of factors associated with in utero passage of meconium (e.g. post term delivery)</td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Resuscitation</td>
<td>Supportive</td>
<td>Resuscitation</td>
</tr>
<tr>
<td></td>
<td>Oxygen</td>
<td>Oxygen if hypoxic</td>
<td>Oxygen</td>
</tr>
<tr>
<td></td>
<td>Ventilation</td>
<td>Ventilator support (e.g. CPAP)</td>
<td>Ventilatory support</td>
</tr>
<tr>
<td></td>
<td>Surfactant (decreases alveolar surface tension, improves lung compliance, and maintains functional residual capacity)</td>
<td>IV fluids and NG tube feeds if too tachypneic to feed orally</td>
<td>Surfactant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Inhaled nitric oxide</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Extracorporeal membrane oxygenation for PPHN</td>
</tr>
</tbody>
</table>
Table 32. Distinguishing Features of RDS, TTN, MAS (continued)

<table>
<thead>
<tr>
<th>Complications</th>
<th>RDS</th>
<th>TTN</th>
<th>MAS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complications</td>
<td>In severe prematurity and/or prolonged ventilation, increased risk of bronchopulmonary dysplasia</td>
<td>Hypoxemia</td>
<td>Hypoxemia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypercapnea</td>
<td>Hypercapnea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Acidois</td>
<td>Acidois</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PPHN</td>
<td>PPHN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pneumothorax</td>
<td>Pneumomediastinum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemical pneumonitis</td>
<td>Secondary surfactant inhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Respiratory failure</td>
<td></td>
</tr>
<tr>
<td>Prognosis</td>
<td>Dependent on GA at birth and severity of underlying lung disease; long-term risks of chronic lung disease</td>
<td>Recovery usually expected in 24-72 h</td>
<td>Dependent on severity, mortality up to 20%</td>
</tr>
</tbody>
</table>

PNEUMONIA
- see Pediatric Respirology, P88
- consider in infants with prolonged or premature rupture of membranes, maternal fever, or if mother is GBS positive
- suspect if infant exhibits respiratory distress, temperature instability, or WBC is low, elevated, or left-shifted
- symptoms may be non-specific
- CXR: hazy lung and/or distinct infiltrates (may be difficult to differentiate from RDS)

Retinopathy of Prematurity
- see Ophthalmology, OP41

Sepsis in the Neonate
Table 33. Sepsis Considerations in the Neonate

<table>
<thead>
<tr>
<th>Early Onset (&lt;72 h)</th>
<th>Late Onset (72 h – 28 d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vertical transmission, 95% present within 24 h after birth</td>
<td>Acquired after birth</td>
</tr>
<tr>
<td>Risk factors:</td>
<td>Most common in preterm infants in NICU (most commonly due to coagulase negative Staphylococcus)</td>
</tr>
<tr>
<td>Maternal infection: UTI, GBS positive, previous child with GBS sepsis or meningitis</td>
<td>Other pathogens implicated include GBS, anaerobes, E. coli, Klebsiella</td>
</tr>
<tr>
<td>Maternal fever/leukocytosis/chorioamnionitis</td>
<td></td>
</tr>
<tr>
<td>Prolonged rupture of membranes (&gt;18 h)</td>
<td></td>
</tr>
<tr>
<td>Preterm labour</td>
<td></td>
</tr>
<tr>
<td>Pathogens: GBS, E. coli, Listeria most common</td>
<td></td>
</tr>
<tr>
<td>Pneumonia more common with early onset sepsis</td>
<td></td>
</tr>
</tbody>
</table>

Signs of Sepsis
- no reliable absolute indicator of occult bacteremia in infants <3 mo, most specific result has been WBC <5
- temperature instability (hypo/hyperthermia)
- respiratory distress, cyanosis, apnea
- tachycardia/bradycardia
- lethargy, irritability
- poor feeding, vomiting, abdominal distension, diarrhea
- hypotonia, seizures, lethargy
- jaundice, hepatomegaly, petechiae, purpura

Chronic Perinatal Infections
- CHEAP TORCHES
  - Chicken pox/shingles
  - Hepatitis B
  - Epstein-Barr virus
  - AIDS (HIV)
  - Parvovirus B19 (erythema infectiosum)
  - Toxoplasmosis
  - Other
  - Rubella virus
  - Cytomegalovirus/Coxsackievirus
  - HSV
  - Every STI
  - Syphilis
- See Obstetrics, OB30
### Skin Conditions of the Neonate

**Table 34. Common Neonatal Skin Conditions**

<table>
<thead>
<tr>
<th>Neonatal Skin Condition</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasomotor Response (Cutis Marmorata, Acrocyanosis)</td>
<td>Transient mottling when exposed to cold; usually normal, particularly if premature</td>
</tr>
<tr>
<td>Vernix Caseosa</td>
<td>Soft, creamy, white layer covering baby at birth</td>
</tr>
<tr>
<td>Congenital Dermal Melanocytosis ('Mongolian Spots')</td>
<td>Slate gray macules over lower back and buttocks (may look like bruises); common in dark skinned infants</td>
</tr>
<tr>
<td>Capillary Hemangioma</td>
<td>Raised red lesion, which increases in size after birth and involutes; 50% resolved by 5 yr, 90% by 9 yr</td>
</tr>
<tr>
<td>Erythema Toxica</td>
<td>Yellow-white papules surrounded by erythema, eosinophils within the lesions; common rash, resolves by 2 wk</td>
</tr>
<tr>
<td>Milia</td>
<td>Lesions 1-2 mm firm white pearly papules on nasal bridge, cheeks, and palate; self-resolving</td>
</tr>
<tr>
<td>Pustular Melanosis</td>
<td>Brown macular base with pustules, seen more commonly in African American infants; may be present at birth</td>
</tr>
<tr>
<td>Nevus Simplex (Salmon Patch)</td>
<td>Transient macular vascular malformation of the eyelids and/or neck (&quot;Angel Kiss&quot; or &quot;Stork Bite&quot;); most lesions disappear by 1 yr of life</td>
</tr>
<tr>
<td>Neonatal Acne</td>
<td>Inflammatory papules and pustules mainly on face; self-resolving</td>
</tr>
</tbody>
</table>

### Fluids and Electrolytes

#### Approach to Infant/Child with Dehydration

**Etiology**
- decreased intake: poor oral intake during acute illness, breastfeeding difficulties, eating disorders
- increased losses: common sites include GI tract (diarrhea, vomiting, bleeding), skin/mucous membranes (fever, burns, hemorrhage, stomatitis), urine (osmotic diuresis [e.g. hyperglycemia, DKA], diuretic therapy, DI, post-obstructive/post ATN recovery diuresis), and respiratory tract (tachypnea, bronchiolitis, pneumonia)

**Management**
- if suspect dehydration based on history (acute illness, decreased number of wet diapers, lethargy, changes in mental status, increased thirst, etc.), you must:
  1. Determine degree of extracellular volume contraction

**Table 35. Assessment of Degree of Extracellular Volume Contraction Based on Physical Exam**

<table>
<thead>
<tr>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2 yr</td>
<td>5%*</td>
<td>10%*</td>
</tr>
<tr>
<td>&gt;2 yr</td>
<td>3%*</td>
<td>6%*</td>
</tr>
<tr>
<td>Pulse</td>
<td>Normal, full</td>
<td>Rapid</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal</td>
<td>Low to normal</td>
</tr>
<tr>
<td>Urine Output</td>
<td>Decreased</td>
<td>Markedly decreased</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>Slightly dry</td>
<td>Dry</td>
</tr>
<tr>
<td>Anterior Fontanelle</td>
<td>Normal</td>
<td>Sunken</td>
</tr>
<tr>
<td>Eyes</td>
<td>Normal</td>
<td>Sunken</td>
</tr>
<tr>
<td>Skin Turgor</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Capillary Refill</td>
<td>Normal (&lt;3 s)</td>
<td>Normal to increased</td>
</tr>
</tbody>
</table>

* Note that percentages refer to percent loss of pre-illness body weight

2) Determine the likely electrolyte disturbance
- dependent on etiology of dehydration and type of fluid loss (isotonic vs. hypertonic vs. hypotonic)
Table 36. Electrolyte Content of Various Bodily Fluids

<table>
<thead>
<tr>
<th>Bodily Fluid</th>
<th>Na⁺ (mmol/L)</th>
<th>K⁺ (mmol/L)</th>
<th>Cl⁻ (mmol/L)</th>
<th>HCO₃⁻ (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saliva</td>
<td>30-80</td>
<td>20</td>
<td>70</td>
<td>30</td>
</tr>
<tr>
<td>Gastric Juice</td>
<td>60-80</td>
<td>15</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Pancreatic Juice</td>
<td>140</td>
<td>5-10</td>
<td>60-90</td>
<td>40-100</td>
</tr>
<tr>
<td>Bile</td>
<td>140</td>
<td>5-10</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>Small Bowel</td>
<td>140</td>
<td>20</td>
<td>100</td>
<td>25-50</td>
</tr>
<tr>
<td>Large Bowel</td>
<td>75</td>
<td>30</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td>Sweat</td>
<td>20-70</td>
<td>5-10</td>
<td>40-60</td>
<td>0</td>
</tr>
</tbody>
</table>

• for moderate and severe dehydration, initial investigations should include urinalysis and blood work examining electrolyte (Na⁺, K⁺, Cl⁻), glucose, and acid-base (blood pH, pCO₂, HCO₃⁻) disturbances, and impaired renal function (creatinine, BUN)

3) Determine if the child requires PO or IV rehydration

• dehydrated child must receive adequate fluid management, including replacement of ongoing losses and maintenance fluids

• ORT indication: mild to moderate dehydration caused by diarrhea
  ■ advantages: ↓ cost, no IV needed, no increase in incidence of iatrogenic hyper/hyponatremia, parental involvement in therapy

• IV rehydration indications: indications for IV rehydration therapy: severe dehydration requiring close monitoring and frequent assessment of electrolytes, inability to tolerate ORT (e.g. vomiting, alteration in mental status, ileus, monosaccharide malabsorption, etc.), inability to provide ORT, failure of ORT in providing adequate rehydration (e.g. persistent diarrhea or vomiting)

4) Return the child to a normal volume and electrolyte status by replacing current deficits and ongoing losses

5) Provide the appropriate fluid and electrolyte maintenance daily requirements

Table 37. Maintenance Fluid Requirements

<table>
<thead>
<tr>
<th>Body Weight</th>
<th>100:50:20 Rule (24 h maintenance fluids)</th>
<th>4:2:1 Rule (hourly rate of maintenance fluids)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-10 kg</td>
<td>100 cc/kg/d</td>
<td>4 cc/kg/h</td>
</tr>
<tr>
<td>11-20 kg</td>
<td>50 cc/kg/d</td>
<td>2 cc/kg/h</td>
</tr>
<tr>
<td>&gt;20 kg</td>
<td>20 cc/kg/d</td>
<td>1 cc/kg/h</td>
</tr>
</tbody>
</table>

• types of fluids used: NS, RL, half NS (0.45% NaCl), 0.2% NS (for neonates only), D5W, and D10W (for neonates only); add potassium chloride if hypokalemic

• in children, all maintenance fluids should have a dextrose component due to their higher risk of hypoglycemia, especially if they are NPO

• common IV fluid combinations used in pediatrics
  ■ first month of life: D5W/0.45 2 NS + KCl 20 mEq/L (only add KCl if voiding well)
  ■ children: D5W/NS + KCl 20 mEq/L or D5W/0.45 NS + KCl 20 mEq/L
  ■ NS: as bolus to restore circulation in dehydrated children (remains almost entirely distributed in intravascular space)
• most important thing to remember when correcting Na aberrations due to fluid deficits
  ▪ risk of cerebral edema with rapid rehydration with hypotonic or isotonic solutions (i.e. NS), therefore replace fluid slowly with close monitoring; aim to adjust (increase or decrease) plasma [Na+] by no more than 12 mmol/L/d
  ▪ management depends on etiology, severity of symptoms, and timing (acute vs. chronic)

6) Continue to monitor fluid and electrolyte status
• accurate monitoring of daily fluid intake (PO and IV) and ongoing losses (urine output, diarrhea, emesis, drains)
• if child receiving >50% of maintenance fluids through IV, serum electrolyte values should be monitored daily and therapy adjusted accordingly
• avoid iatrogenic hyper/hyponatremia, keep the possibility of SIADH in mind

Nephrology

Common Pediatric Renal Diseases

Table 38. Common Manifestations of Renal Disease

<table>
<thead>
<tr>
<th>Neonate</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flank Mass</td>
<td>Hydronephrosis, polycystic disease (autosomal dominant or recessive subtypes), tumour</td>
</tr>
<tr>
<td>Hematuria</td>
<td>Renal vein thrombosis, asphyxia, malformation, trauma</td>
</tr>
<tr>
<td>Anuria/Oliguria</td>
<td>Bilateral renal agenesis, obstruction, asphyxia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Child and Adolescent</th>
<th>Common Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cola/Red-Coloured Urine</td>
<td>Acute GN (post-streptococcal, HSP, IgA nephropathy, etc.), hemoglobinuria (hemolyis), myoglobinuria (rhabdomyolysis)</td>
</tr>
<tr>
<td>Gross Hematuria</td>
<td>Urologic disease (nephrolithiasis, trauma, etc.), UTI, acute GN</td>
</tr>
<tr>
<td>Edema</td>
<td>Nephrotic syndrome, nephritis, acute/chronic renal failure, consider cardiac or liver disease</td>
</tr>
<tr>
<td>HTN</td>
<td>GN, renal failure, dysplasia (consider coarctation, drugs, endocrine causes)</td>
</tr>
<tr>
<td>Polyuria</td>
<td>DM, central and nephrogenic DI, renal Fanconi’s syndrome (genetic/metabolic/acquired causes), hypercalcemia, polyuric renal failure (renal dysplasia)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>Osteostatic, nephrotic syndrome (MCD, etc.), GN</td>
</tr>
<tr>
<td>Oliguria</td>
<td>Dehydration, ATN, interstitial nephritis, acute or chronic kidney disease (i.e. renal failure)</td>
</tr>
<tr>
<td>Urgency</td>
<td>UTI, vulvovaginitis</td>
</tr>
</tbody>
</table>

Hemolytic Uremic Syndrome

Definition
• simultaneous occurrence of the triad of 1) non-immune microangiopathic hemolytic anemia, 2) thrombocytopenia, and 3) acute renal injury

Epidemiology
• annual incidence of 1-2 per 100,000 in Canada
• most common cause of acute renal failure in children

Etiology
• diarrhea positive HUS: 90% of pediatric HUS from E. coli O157:H7, shiga toxin, or verotoxin
• diarrhea negative HUS: other bacteria, viruses, drugs, familial/genetic

Pathophysiology
• toxin binds, invades, and destroys colonic epithelial cells, causing bloody diarrhea
• toxin enters the systemic circulation, attaches to, and injures endothelial cells (especially in kidney), causing a release of endothelial products (e.g. von Willebrand factor, platelet aggregating factor)
• platelet/fibrin thrombi form in multiple organ systems (e.g. kidney, pancreas, brain, etc.) resulting in thrombocytopenia
• RBCs are forced through occluded vessels, resulting in fragmented RBCs (schistocytes) that are removed by the reticuloendothelial system (hemolytic anemia)
History and Physical Exam

- history: initial presentation of abdominal pain and diarrhea, followed by bloody diarrhea; within 5-7 days begins to show signs of anemia, thrombocytopenia, and renal insufficiency
- physical exam: pallor, jaundice (hemolysis), edema, petechiae, HTN

Investigations

- CBC (anemia, thrombocytopenia), blood smear (schistocytes), electrolytes, renal function, urinalysis (microscopic hematuria), stool cultures, and verotoxin/shigella toxin assay

Management

- mainly supportive: nutrition, hydration, ventilation (if necessary), blood transfusion for symptomatic anemia
- monitor electrolytes and renal function: dialysis if electrolyte abnormality (hyperkalemia) cannot be corrected, fluid overload, or uremia
- steroids are not helpful
- antibiotics are contraindicated because death of bacteria leads to increased toxin release and worse clinical course

Prognosis

- <5% mortality, 5-25% long-term renal damage (HTN, proteinuria, decreased renal function)

Nephritic Syndrome

Definition

- acute or chronic syndrome affecting the kidney, characterized by glomerular injury and inflammation, and defined by hematuria (>5 RBCs per high-powered microscope field) and the presence of dysmorphic RBCs and RBC casts on urinalysis
- often accompanied by at least one of proteinuria (<50 mg/kg/d), edema, HTN, azotemia, and oliguria

Epidemiology

- highest incidence in children aged 5-15 yr old

Etiology

- humoral immune response to a variety of etiologic agents → immunoglobulin deposition → complement activation, leukocyte recruitment, release of growth factors/cytokines → glomerular inflammation and injury → porous podocytes → hematuria + RBC casts ± proteinuria
- HTN secondary to fluid retention and increased renin secretion by ischemic kidneys

Table 39. Major Causes of Nephritic Syndrome

<table>
<thead>
<tr>
<th>Decreased C3</th>
<th>Normal C3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary (idiopathic)</td>
<td></td>
</tr>
<tr>
<td>Post-infectious GN (most common cause of acute GN in pediatrics)</td>
<td>IgA nephropathy</td>
</tr>
<tr>
<td>Membranoproliferative</td>
<td>Idiopathic rapidly progressive GN</td>
</tr>
<tr>
<td>• Type I (50-80%)</td>
<td>Anti-GBM disease</td>
</tr>
<tr>
<td>• Type II (&gt;80%)</td>
<td></td>
</tr>
<tr>
<td>Secondary (systemic disease)</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>HSP (very common)</td>
</tr>
<tr>
<td>Bacterial endocarditis</td>
<td>Polycartitis nodosa</td>
</tr>
<tr>
<td>Abscess or shunt nephritis</td>
<td>Granulomatosis with polyangiitis</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Goodpasture’s syndrome</td>
</tr>
</tbody>
</table>

Risk Factors

- see Major Causes of Nephritic Syndrome, above

History and Physical Exam

- often asymptomatic; some overlap in clinical findings for nephritic and nephrotic syndrome
- gross hematuria, mild-moderate edema, oliguria, HTN
- signs and symptoms suggestive of underlying systemic causes (e.g. fever, arthralgias, rash, dyspnea, pulmonary hemorrhage)

Investigations

- urine
  - dipstick (hematuria, 0 to 2+ proteinuria) and microscopy (>5 RBCs per high-powered microscope field, acanthocytes, RBC casts)
  - first morning urine protein/creatinine ratio (<200 mg/mmol)
blood work
- impaired renal function (↑ Cr and BUN) resulting in ↓ pH and electrolyte abnormalities (hyperkalemia, hyperphosphatemia, hypocalcemia)
- mild anemia on CBC (secondary to hematuria)
- hypoalbuminemia (secondary to proteinuria)
- appropriate investigations to determine etiology: C3/C4 levels, serologic testing for recent streptococcal infection (ASOT, anti-hyaluronidase, anti-streptokinase, anti-NAD, anti-DNase B), ANA, anti-DNA antibodies, ANCA, serum IgA levels, anti-GBM antibodies
- renal biopsy should be considered only in the presence of acute renal failure, no evidence of streptococcal infection, normal C3/C4

Management
- treat underlying cause
- symptomatic
  - renal insufficiency: supportive (dialysis if necessary), proper hydration
  - HTN: salt and fluid restriction (but not at expense of renal function), ACE inhibitors or ARBs for chronic persistent HTN (not acute cases because ACE inhibitors or ARBs may decrease GFR further)
  - edema: salt and fluid restriction, possibly diuretics (avoid if significant intravascular depletion)
  - corticosteroids if indicated: IgA nephropathy, lupus nephritis, etc.

Prognosis
- dependent on underlying etiology
- complications include HTN, heart failure, pulmonary edema, chronic kidney injury (requiring renal transplant)

Nephrotic Syndrome

Definition
- clinical syndrome affecting the kidney, characterized by significant proteinuria, peripheral edema, hypoalbuminemia, and hyperlipidemia

Epidemiology
- highest incidence in children 2-6 yr old, M>F

Etiology
- primary (idiopathic): nephrotic syndrome in the absence of systemic disease (most common cause in pediatrics)
  - glomerular inflammation ABSENT on renal biopsy: MCD (85%), focal segmental glomerular sclerosis
  - glomerular inflammation PRESENT on renal biopsy: membranoproliferative GN, IgA nephropathy
- secondary: nephrotic syndrome associated with systemic disease or due to another process causing glomerular injury (<10% in pediatrics)
  - autoimmune: SLE, DM, rheumatoid arthritis
  - genetic: sickle cell disease, Alport syndrome
  - infections: hepatitis B/C, post-streptococcal, infective endocarditis, HUS, HIV
  - malignancies: leukemia, lymphoma
  - medications: captopril, penicillamine, NSAIDs, antiepileptics
  - vasculitides: HSP, granulomatosis with polyangiitis
- congenital: congenital nephropathy of the Finnish type, Denys-Drash syndrome, etc.

Risk Factors
- family history, certain systemic illnesses and medications (as per Etiology)

History and Physical Exam
- non-specific symptoms such as irritability, malaise, fatigue, anorexia, or diarrhea
- edema
  - often first sign; detectable when fluid retention exceeds 3-5% of body weight
  - starts periorbital and often pretilal → edematous areas are white, soft, and pitting
  - gravity dependent: periorbital edema ↓ and pretilial edema ↑ over the day
  - anasarca may develop (i.e. marked periorbital and peripheral edema, ascites, pleural effusions, scrotal/labial edema)
  - decrease in effective circulating volume (e.g. tachycardia, HTN, oliguria, etc.)
- foamy urine is a possible sign of proteinuria
Investigations
- urine
  - urine dipstick (3 to 4+ proteinuria, microscopic hematuria) and microscopy (oval fat bodies, hyaline casts)
  - first morning urine protein/creatinine ratio (>200 mg/mmol)
- blood work
  - diagnostic: hypoalbuminemia (<25 g/L), hyperlipidemia/hypercholesterolemia (total cholesterol >5 mmol/L)
  - secondary: electrolytes (hypocalcemia, hyperkalemia, hyponatremia), renal function (↑ BUN and Cr), coagulation profile (↓ PTT)
  - appropriate investigations to rule out secondary causes: CBC, blood smear, C3/C4, ANA, hepatitis B/C titres, ASOT, HIV serology, etc.
- consider renal biopsy if: HTN, gross hematuria, ↓ renal function, low serum C3/C4, no response to steroids after 4 wk of therapy, frequent relapses (>2 in 6 mo), presentation before first year of life (high likelihood of congenital nephrotic syndrome), presentation ≥12 yr (rule out more serious renal pathology than MCD)

Management
- MCD: oral prednisone 2 mg/kg/d (or equivalent) for up to 12 wk → varicella status should be known before starting
- consider cytotoxic agents, immunomodulators, or high-dose pulse corticosteroid if steroid resistant
- symptomatic
  - edema: salt and fluid restriction, possibly diuretic (avoid if significant intravascular depletion); furosemide + albumin for anasarca
  - hyperlipidemia: generally resolves with remission; limit dietary fat intake; consider statin therapy if persistently nephrotic
  - hypoaalbuminemia: IV albumin and furosemide not routinely given; consider if refractory edema
  - abnormal BP: control BP; fluid resuscitation if severe intravascular depletion; ACE inhibitors or ARBs for persistent HTN
- diet: no added salt; monitor caloric intake and supplement with Ca²⁺ and Vit D if on corticosteroids
- daily weights and BP to assess therapeutic progress
- secondary infections: treat with appropriate antimicrobials; antibiotic prophylaxis not recommended; pneumococcal vaccine at diagnosis and varicella vaccine after remission; varicella Ig + acyclovir if exposed while on corticosteroids
- secondary hypercoagulability: mobilize, avoid hemoconcentration due to hypovolemia, prompt sepsis treatment; heparin if thrombi occur

Prognosis
- generally good: 80% of children responsive to corticosteroids
- up to 2/3 experience relapse, often multiple times; sustained remission with normal kidney function usually by adolescence
- complications: ↑ risk of infections (spontaneous peritonitis, cellulitis, sepsis); hypercoagulability due to decreased intravascular volume and antithrombin III depletion (PE, renal vein thrombosis); intravascular volume depletion, leading to hypotension, shock, renal failure; side effects of drugs

Hypertension in Childhood

Definition
- HTN: sBP and/or dBP ≥95th percentile for sex, age, and height on ≥3 occasions
- pre-HTN: sBP and/or dBP ≥90th percentile but <95th percentile OR BP ≥120/80 irrespective of age, gender, and height

<table>
<thead>
<tr>
<th>Table 40. 95th Percentile Blood Pressures (mmHg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Yr)</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>12</td>
</tr>
<tr>
<td>17</td>
</tr>
</tbody>
</table>

Epidemiology
• prevalence: 3-5% for HTN, 7-10% for pre-HTN; M>F
• increasing prevalence of pre-HTN over the last 25+ years

Etiology
• primary HTN
  • diagnosis of exclusion
  • most common in older children (≥10 yr), especially if positive family history, overweight, and only mild HTN
  • responsible for ~90% of cases of HTN in adolescents, rarely in young children
• secondary HTN
  • identifiable cause of HTN (most likely etiology depends on age)
  • responsible for majority of childhood HTN
• always consider white coat HTN for all ages

<table>
<thead>
<tr>
<th>Table 41. Etiology of Secondary HTN by Age Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>System</td>
</tr>
<tr>
<td>--------</td>
</tr>
<tr>
<td>Endocrine/Metabolic</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Vascular</td>
</tr>
<tr>
<td>Drugs</td>
</tr>
</tbody>
</table>

*Risk Factors
• primary HTN: male gender, positive family history, obesity, obstructive sleep apnea, African American, prematurity/LBW
• secondary HTN: history of renal disease, abdominal trauma, family history of autoimmune diseases, umbilical artery catheterization

History
• often asymptomatic, but can include FTT, fatigue, epistaxis
• symptoms of hypertensive emergency
  • neurologic: headache, seizures, local complaints, change in mental status, visual disturbances
  • cardiovascular: symptoms of MI or heart failure (chest pain, palpitations, cough, SOB)
• symptoms of secondary HTN: guided by etiology; ask about medications and recreational drugs (current and past)

Physical Exam
• BP measurement (make sure correct cuff size is used), plot on growth chart, BMI
• look for signs of hypertensive emergency (e.g. full neurologic exam, ophthalmoscopy, precordial exam, peripheral pulses, perfusion status)
• look for signs of secondary HTN

Investigations
• laboratory
  • urine dipstick for hematuria and/or proteinuria (renal disease), urine catecholamines (pheochromocytoma, neuroblastoma)
  • blood work: renal function tests (electrolytes, Cr, BUN), consider renin and aldosterone levels (RAS, Conn's syndrome, Wilms' tumour)
  • other specific hormones if indicated on history and physical
  • imaging: Echo (coarctation, heart function), abdominal U/S (RAS, abdominal mass), renal radionucleide imaging (renal scarring)
  • other: ocular exam

Management
• treat underlying cause
• non-pharmacologic: modify concurrent cardiovascular risk factors (weight reduction, exercise, salt restriction, smoking cessation)
• pharmacologic: gradual lowering of BP using thiazide diuretics; no antihypertensives have been formally studied in children; if hypertensive emergencies use hydralazine, labetalol, sodium nitroprusside
• management of end-organ damage (e.g. retinopathy, LVH)
• consider referral to specialist
Prognosis
• end-organ damage (similar to adults) including LVH, CHF, cerebrovascular insults, renal disease, retinopathy

Neurology

Seizure Disorders

Differential Diagnosis of Seizures in Children
• benign febrile seizure
• CNS: infection, tumour, HIE, trauma, hemorrhage
• metabolic: hypoglycemia, hypocalcemia, hyponatremia
• idiopathic epilepsy and epileptic syndromes
• others: neurocutaneous syndromes, AVM, drug ingestions/withdrawal
• seizure mimics

Investigations
• lab tests: CBC, electrolytes, calcium, magnesium, glucose
• toxicology screen if indicated
• EEG
• CT/MRI, if indicated (focal neurological deficit or has not returned to baseline several hours after seizure)
• consider LP if first-time non-febrile seizure (not indicated for determining recurrence risk of benign febrile seizures or to determine seizure type or epileptic syndrome)

CHILDHOOD EPILEPTIC SYNDROMES

Infantile Spasms
• brief, repeated symmetric contractions of neck, trunk, extremities (flexion and extension) lasting 10-30 s
• occur in clusters; often associated with developmental delay; onset 4-8 mo
• 20% unknown etiology (usually good response to treatment); 80% due to metabolic or developmental abnormalities, encephalopathies, or are associated with neurocutaneous syndromes (usually poor response to treatment)
• can develop into West syndrome (infantile spasms, psychomotor developmental arrest, and hyperarrhythmia) or Lennox-Gastaut (see below)
• typical EEG: hyperarrhythmia (high voltage slow waves, spikes and polyspikes, background disorganization)
• management: ACTH, vigabatrin, benzodiazepines

Lennox-Gastaut
• characterized by triad of 1) multiple seizure types, 2) diffuse cognitive dysfunction, and 3) slow generalized spike and slow wave EEG
• onset commonly 3-5 yr of age
• seen with underlying encephalopathy and brain malformations
• management: valproic acid, benzodiazepines, and ketogenic diet; however, response often poor

Juvenile Myoclonic Epilepsy (Janz Syndrome)
• myoclonus particularly in morning; frequently presents as generalized tonic-clonic seizures
• adolescent onset (12-16 yr of age); autosomal dominant with variable penetrance
• typical EEG: 3.5-6 Hz irregular spike and wave, increased with photic stimulation
• management: lifelong treatment (valproic acid); excellent prognosis

Childhood Absence Epilepsy
• multiple daily absence seizures lasting <30 s without post-ictal state that may resolve spontaneously or become generalized in adolescence
• peak age of onset 6-7 yr, F>M, strong genetic predisposition
• typical EEG: 3 Hz spike and wave
• management: valproic acid or ethosuximide

Heart problems, such as long QT syndrome and hypertrophic cardiomyopathy, are often misdiagnosed as epilepsy. Include cardiac causes of syncope in your differential diagnosis, particularly when the episodes occur during physical activity.

Seizure Mimics
• Benign paroxysmal vertigo
• Breath holding
• Hypoglycemia
• Narcolepsy
• Night terror
• Pseudoseizure
• Syncope
• TIA
• Tic
Benign Focal Epilepsy of Childhood with Rolandic/Centrotemporal Spikes

- focal motor seizures involving tongue, mouth, face, upper extremity usually occurring in sleep-wake transition states; remains conscious, but aphasic post-ictally
- onset peaks at 5-10 yr of age; 16% of all non-febrile seizures; remits spontaneously in adolescence without sequelae
- typical EEG: repetitive spikes in centrotemporal area with normal background
- management: frequent seizures controlled by carbamazepine, no medication if infrequent seizures

General Approach to Treatment

- education for patient and parents including education and precautions in daily life (e.g. buddy system, showers instead of baths)
- medication
  - initiate: treatment with drug appropriate to seizure type; often if >2 unprovoked afebrile seizures within 6-12 mo
  - optimize: start with one drug and increase dosage until seizures controlled
  - if no effect, switch over to another before adding a second antiepileptic drug
  - continue antiepileptic drug therapy until patient free of seizures for >2 yr, then wean over 4-6 mo
- ketogenic diet (high fat diet): used in patients who do not respond to polytherapy or who do not wish to take medication (valproic acid contraindicated in conjunction with ketogenic diet because may increase hepatotoxicity)
- legal obligation to report to Ministry of Transportation if patient wishes to drive

Generalized and Partial Seizures

- see Neurology, N18

Febrile Seizures

Epidemiology

- most common cause of seizure in children (3-5% of children)
- M>F; age 6 mo-6 yr

Clinical Presentation

- often with associated illness or fever and family history
- no evidence of CNS infection/inflammation before or after seizure; no history of non-febrile seizures

Table 42. Comparison of Typical and Atypical Febrile Seizures

<table>
<thead>
<tr>
<th>Simple/Typical (70-80%)</th>
<th>Complex/Atypical (20-30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All of the following:</td>
<td>At least one of the following:</td>
</tr>
<tr>
<td>• Duration &lt;15 min (95% &lt;5 min)</td>
<td>• Duration &gt;15 min</td>
</tr>
<tr>
<td>• Generalized tonic-clonic</td>
<td>• Focal onset or focal features during seizure</td>
</tr>
<tr>
<td>• No recurrence in 24 h period</td>
<td>• Recurrent seizures (&gt;1 in 24 h period)</td>
</tr>
<tr>
<td>• No neurological impairment or developmental delay before or after seizure</td>
<td>• Previous neurological impairment or neurological deficit after seizure</td>
</tr>
</tbody>
</table>

Workup

- history: determine focus of fever, description of seizure, medications, trauma history, development, family history
- physical exam: LOC, signs of meningitis, neurological exam, head circumference, focus of infection
- septic workup including LP if suspecting meningitis (strongly consider if child <12 mo; consider if child is 12-18 mo; only if meningeal signs present if child >18 mo)
- if typical febrile seizure, investigations only for determining focus of fever
- EEG/CT/MRI brain not warranted unless atypical febrile seizure or abnormal neurologic findings

Management

- counsel and reassure patient and parents
  - febrile seizures do not cause brain damage
  - very small risk of developing epilepsy; 9% in child with multiple risk factors; 2% in child with typical febrile seizures compared to 1% in general population
  - 33% chance of recurrence (mostly within 1 yr of first seizure and in children <1 yr old)
  - antipyretics and fluids for comfort (though neither prevent seizure)
• prophylaxis with antiepileptic drugs not recommended
• if high risk for recurrent or prolonged seizures, have rectal or sublingual lorazepam at home
• treat underlying cause of fever

### Recurrent Headache

- see Neurology, N45

### Differential Diagnosis

- primary headache: tension, migraine, cluster
- secondary headache: see Neurology, N45

### General Assessment

- if unremarkable history and neurological and general physical exam is negative, most likely diagnosis is migraine or tension headache
- CT or MRI if history or physical reveals red flags
- inquire about level of disability, academic performance, after-school activities

### Hypotonia

- decreased resistance to passive movements – “floppy baby”

### Differential Diagnosis

- central: chromosomal (DS, Prader-Willi, Fragile X syndrome), metabolic (hypoglycemia, kernicterus), perinatal problems (asphyxia, ICH), endocrine (hypothyroidism, hypopituitarism), systemic illness (TORCH infection, sepsis, dehydration), CNS malformations, dysmorphic syndromes
- peripheral: motor neuron (spinal muscular atrophy, polio), peripheral nerve (Charcot-Marie-Tooth syndrome) neuromuscular junction (myasthenia gravis), muscle fibre (mitochondrial myopathy, muscular dystrophy, myotonic dystrophy)

### History and Physical Exam

- proper assessment of tone requires accurate determination of GA
- differentiate between UMN and LMN lesion: spontaneous posture (spontaneous movement, movement against gravity, frog-leg position); muscle weakness; joint mobility (hyperextensibility); muscle bulk; presence of fasciculations
- postural maneuvers
  - traction response: pull to sit, look for flexion of arms to counteract traction and head lag
  - axillary suspension: suspend infant by holding at axilla and lifting; hypotonic babies will slip through grasp because of low shoulder girdle tone
  - ventral suspension: infant is prone and supported under the abdomen by one hand; infant should be able to hold up extremities; inverted “U” posturing demonstrates hypotonia
- dysmorphic features, cognitive ability, reflexes, strength

### Investigations

- rule out systemic disorders (e.g. electrolytes, ABG, blood glucose, CK, and serum/urine investigations for multiple etiologies including mitochondrial causes)
- neuroimaging: MRI/MRA when indicated
- EMG, muscle biopsy/NCS
- chromosome analysis, genetic testing, metabolic testing, neuromuscular testing

### Treatment

- depends on etiology: some treatments available for specific diagnosis
- counsel parents on prognosis and genetic implications
- refer patients for specialized care, refer for rehabilitation, OT, PT, assess feeding ability

### Cerebral Palsy

#### Definition

- a symptom complex, not a disease
- non-progressive central motor impairment syndrome due to insult to or anomaly of the immature CNS
- incidence: 1.5-2.5/1,000 live births (industrialized nations)
- life expectancy is dependent on the degree of mobility and intellectual impairment, not on severity of CNS lesion
Etiology
• often obscure, no definite etiology identified in 1/3 of cases
• 10% related to intrapartum asphyxia; 10% due to postnatal insult (infections, asphyxia, prematurity with IVH and trauma)
• association with LBW babies

Clinical Presentation
• general signs: delay in motor milestones, developmental delay, learning disabilities, visual/hearing impairment, seizures, microcephaly, uncoordinated swallow (aspiration)

Table 43. Types of Cerebral Palsy

<table>
<thead>
<tr>
<th>Type</th>
<th>% of Total</th>
<th>Characteristics</th>
<th>Area of Brain Involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spastic</td>
<td>70-80%</td>
<td>Truncal hypotonia in first yr Increased tone, increased reflexes, clonus</td>
<td>UMN of pyramidal tract</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can affect one limb (monoplegia), one side of body (hemiplegia), both legs (diplegia), or both arms and legs (quadriplegia)</td>
<td>Diplegia associated with periventricular leukomalacia in premature babies</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Quadriplegia associated with HIE (asphyxia), higher incidence of intellectual disability</td>
</tr>
<tr>
<td>Athetoid/Dyskinetic</td>
<td>10-15%</td>
<td>Athetosis (involuntary writhing movements) Chorea (involuntary jerky movements) Can involve face, tongue (results in dystonia)</td>
<td>Basal ganglia (may be associated with kernicterus)</td>
</tr>
<tr>
<td>Ataxic</td>
<td>&lt;5%</td>
<td>Poor coordination, poor balance (wide based gait)</td>
<td>Cerebellum</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can have intention tremor</td>
<td></td>
</tr>
<tr>
<td>Mixed</td>
<td>10-15%</td>
<td>More than one of the above motor patterns</td>
<td></td>
</tr>
</tbody>
</table>

Investigations
• may include metabolic screen, chromosome studies, serology, neuroimaging (MRI), EMG, EEG (if seizures), ophthalmology assessment, audiology assessment

Treatment
• maximize potential through multidisciplinary services such as primary care physician, OT, PT, SLP, school supports, etc.
• orthopedic management (e.g. dislocations, contractures, rhizotomy)
• management of symptoms: spasticity (baclofen, Botox®), constipation (stool softeners)

Neurocutaneous Syndromes
• characterized by tendency to form tumours of the CNS, PNS, viscera, and skin

NEUROFIBROMATOSIS TYPE I
• autosomal dominant but 50% are the result of new mutations
• also known as von Recklinghausen disease
• incidence 1:3,000, mutation in NFI gene on 17q11.2 (codes for neurofibromin protein)
• learning disorders, abnormal speech development, and seizures are common
• diagnosis of NF-1 requires 2 or more of:
  - ≥6 café-au-lait spots (>5 mm if prepubertal, >1.5 cm if postpubertal)
  - ≥2 neurofibromas of any type or one plexiform neurofibroma
  - ≥2 Lisch nodules (hamartomas of the iris)
  - optic glioma
  - freckling in the axillary or inguinal region
  - a distinctive bony lesion (e.g. sphenoid dysplasia, cortical thinning of long bones)
  - a first degree relative with confirmed NF-1

NEUROFIBROMATOSIS TYPE II
• autosomal dominant
• incidence 1:33,000
• characterized by predisposition to form intracranial, spinal tumours
• diagnosed when bilateral vestibular schwannomas are found, or a first-degree relative with NF-2 and either unilateral vestibular schwannoma, or any two of the following: meningioma, glioma, schwannoma, neurofibroma, posterior subcapsular lenticular opacities.
• treatment consists of monitoring for tumour development and surgery
**Respirology**

**Approach to Dyspnea**

- determine if patient is sick or not sick; ABCs
- history: onset, previous episodes, precipitating events, associated symptoms, past medical/family history of respiratory disease
- physical exam: vitals, SpO2, evidence of cyanosis, respiratory, cardiovascular
- investigations: CBC and differential, electrolytes, BUN, Cr, NP swab, ABG, CXR, ECG (based on clinical findings)

![Figure 16. Approach to dyspnea in childhood](image)

**Upper Respiratory Tract Diseases**

- see Otolaryngology, OT44
- diseases above the thoracic inlet characterized by inspiratory stridor, hoarseness, and suprasternal retractions
- differential diagnosis of stridor: croup, bacterial tracheitis, epiglottitis, foreign body aspiration, subglottic stenosis (congenital or iatrogenic), laryngomalacia/tracheomalacia (collapse of airway cartilage on inspiration)

<table>
<thead>
<tr>
<th>Table 44. Common Upper Respiratory Tract Infections in Children</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Croup (Laryngotracheobronchitis)</strong></td>
</tr>
<tr>
<td><strong>Anatomy</strong></td>
</tr>
<tr>
<td><strong>Epidemiology</strong></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
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<tr>
<td><strong>Clinical Presentation</strong></td>
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<td></td>
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<tr>
<td><strong>Investigations</strong></td>
</tr>
<tr>
<td></td>
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<tr>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
</tbody>
</table>
Lower Respiratory Tract Diseases

- obstruction of airways below thoracic inlet, produces more expiratory sounds
- classic symptom: wheezing

Differential Diagnosis of Wheezing

- common: asthma (recurrent wheezing episodes, identifiable triggers, typically over 6 yr), bronchiolitis (first episode of wheezing, usually under 1 yr), recurrent aspiration (often neurological impairment), pneumonia (fever, cough, malaise)
- uncommon: foreign body (acute unilateral wheezing and coughing), CF (prolonged wheezing, unresponsive to therapy), bronchopulmonary dysplasia (often develops after prolonged ventilation in the newborn)
- rare: CHF, mediastinal mass, bronchiolitis obliterans, tracheobronchial anomalies

Pneumonia

Etiology
- inflammation of pulmonary tissue, associated with consolidation of alveolar spaces

Clinical Presentation
- incidence is greatest in first year of life with viral causes being most common in children <5 yr
- fever, cough, tachypnea
- CXR: diffuse, streaky infiltrates bilaterally
- bacterial causes may present with cough, fever, chills, dyspnea, more dramatic CXR changes (e.g. lobar consolidation, pleural effusion)

Management
- supportive therapy: hydration, antipyretics, humidified O₂

Table 45. Common Causes and Treatment of Pneumonia at Different Ages

<table>
<thead>
<tr>
<th>Age</th>
<th>Bacterial</th>
<th>Viral</th>
<th>Atypical Bacteria</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>GBS</td>
<td>CMV Herpes virus</td>
<td>Mycoplasma hominis Ureaplasma urealyticum</td>
<td>Ampicillin + gentamicin / tobramycin (add erythromycin if suspect Chlamydia)</td>
</tr>
<tr>
<td>1-3 mo</td>
<td>S. aureus</td>
<td>CMV, RSV Influenza</td>
<td>Chlamydia trachomatis Ureaplasma urealyticum</td>
<td>Cefuroxime OR ampicillin ± erythromycin OR clarithromycin</td>
</tr>
<tr>
<td>3 mo-5 yr</td>
<td>S. pneumoniae</td>
<td>RSV Adenovirus</td>
<td>Mycoplasma pneumoniae TB</td>
<td>Amoxicillin (if mild) OR ampicillin OR cefuroxime</td>
</tr>
<tr>
<td>&gt;5 yr</td>
<td>S. pneumoniae</td>
<td>Influenza</td>
<td>Mycoplasma pneumoniae</td>
<td>Erythromycin OR clarithromycin (1st line) OR ampicillin OR cefuroxime</td>
</tr>
<tr>
<td></td>
<td>H. influenzae</td>
<td></td>
<td>Chlamydia pneumoniae TB</td>
<td></td>
</tr>
</tbody>
</table>

Bronchiolitis

Definition
- LRTI, usually in children <2 yr, that has wheezing and signs of respiratory distress

Epidemiology
- the most common LRTI in infants, affects 50% of children in first 2 yr of life; peak incidence at 6 mo, winter or early spring
- increased incidence of asthma in later life

Etiology
- RSV (>50%), parainfluenza, influenza, rhinovirus, adenovirus, M. pneumoniae (rare)

Clinical Presentation
- prodrome of URTI with cough and/or rhinorrhea, possible fever
- feeding difficulties, irritability
- wheezing, crackles, respiratory distress, tachypnea, tachycardia, retractions, poor air entry; symptoms often peak at 3-4 d

Bronchodilators for Bronchiolitis
Cochrane DB Syst Rev 2010;12:CD001266
Study: Meta-analysis of prospective, randomized, double-blinded, placebo-controlled trials.
Patients: 1,912 infants (28 trials) up to 24 mo old with bronchiolitis.
Intervention: Bronchodilators (including albuterol, salbutamol, terbutaline, ipratropium bromide, and adrenergic agonists given oral, subcutaneous, or nebulized vs. placebo.
Main Outcome: Oxygen saturation.
Results: No clinically significant difference for infants treated with bronchodilators vs. placebo for bronchiolitis. Given the costs and side effects, it is not recommended to use bronchodilators as management for bronchiolitis in infants.
Investigations

- CXR (only in severe disease, poor response to therapy, chronic episode): air trapping, peribronchial thickening, atelectasis, increased linear markings
- NP swab: direct detection of viral antigen (immuno fluorescence)
- WBC can be normal

Treatment

- self-limiting disease with peak symptoms usually lasting 2-3 wk
- mild to moderate distress
  - supportive: PO or IV hydration, antipyretics for fever, regular or humidified high flow O₂
  - severe distress
    - as above ± intubation and ventilation as needed
    - consider rebetol (Ribavirin®) in high risk groups: bronchopulmonary dysplasia, CHD, congenital lung disease, immunodeficient
- monthly RSV-Ig or palivizumab (monoclonal antibody against the F-glycoprotein of RSV) is protective against severe disease in high risk groups; case fatality rate <1%
- antibiotics have no therapeutic value unless there is secondary bacterial pneumonia
  - indications for hospitalization
    - hypoxia: O₂ saturation <92% on initial presentation
    - persistent resting tachypnea >60/min and retractions after several salbutamol masks
    - past history of chronic lung disease, hemodynamically significant cardiac disease, neuromuscular problem, immunocompromised
    - young infants <6 mo old (unless extremely mild)
    - significant feeding problems
    - social problem (e.g. inadequate care at home)

Asthma

Definition

- see Respirology, R7
- characterized by recurrent episodes of airway hyperreactivity, bronchospasm, and inflammation; reversible small airway obstruction
- very common, presents most often in early childhood
- associated with other atopic diseases such as allergic rhinitis or atopid dermatitis

Clinical Presentation

- episodic bouts of wheezing, dyspnea, tachypnea, cough (usually at night/early morning, with activity, or cold exposure)
- physical exam may reveal hyper-resonant chest, prolonged expiration, wheeze

Triggers

- URTI (viral or Mycoplasma), weather (cold exposure, humidity changes), allergens (pets), irritants (cigarette smoke), exercise, emotional stress, drugs (ASA, β-blockers)

Classification

- mild: occasional attacks of wheezing or coughing (<2/wk); symptoms respond quickly to inhaled bronchodilator; never needs systemic corticosteroids
- moderate: more frequent episodes with symptoms persisting and chronic cough; decreased exercise tolerance; sometimes needs systemic corticosteroids
- severe: daily and nocturnal symptoms; frequent ED visits and hospitalizations; usually needs systemic corticosteroids

Management

- acute
  - O₂ (keep O₂ saturation >94%) and fluids if dehydrated
  - β₂-agonists: salbutamol (Ventolin®) MDI + spacer (nebulized or IV in very severe episodes with impending respiratory failure), 5 puffs (<20 kg) or 10 puffs q20min for first hour (>20 kg)
  - ipratropium bromide (Atrovent®) if severe: MDI + spacer, 3 puffs (<20 kg) or 6 puffs (>20 kg) q20min with salbutamol, or add to first 3 salbutamol masks (0.25 mg if <20 kg, 0.5mg if >20 kg)
  - steroids: prednisone (1-2 mg/kg x 5 d) or dexamethasone (0.3 mg/kg/d x 5 d or 0.6 mg/kg/d x 2 d); in severe disease, use IV steroids
  - continue to observe; can discharge patient if asymptomatic for 2-4 h after last dose
- chronic
  - education, emotional support, avoid allergens or irritants, develop an “action plan”
  - exercise program (e.g. swimming)
  - monitor respiratory function with peak flow meter (improves self-awareness of status)

Canadian Pediatric Asthma Consensus Guidelines for Assessing Adequate Control of Asthma

- Daytime symptoms <4 d/wk
- Night time symptoms <1 night/wk
- Normal physical activity
- Mild and infrequent exacerbations
- No work/school absenteeism
- Need for β-agonist <4 doses/wk
- FEV₁ or peak expiratory flow ≥90% of personal best
- Peak expiratory flow diurnal variation ≤10-15%
PFTs for children >6 yr
- reliever therapy: short acting β₂-agonists (e.g. salbutamol)
- controller therapy (first line therapy for all children): low dose daily inhaled corticosteroids
- second line therapy for children <12 yr: moderate dose of daily inhaled corticosteroids
- second line therapy for children >12 yr: leukotriene receptor antagonist OR long acting β₂-agonist in conjunction with low dose inhaled corticosteroids; leukotriene receptor antagonist monotherapy may be considered an alternative second line therapy
- severe asthma unresponsive to first and second line treatments: injection immunotherapy
- aerochamber for children using daily inhaled corticosteroids

indications for hospitalization
- ongoing need for supplemental O₂
- persistently increased work of breathing
- β₂-agonists are needed more often than q4h after 4-8 h of conventional treatment
- patient deteriorates while on systemic steroids

Cystic Fibrosis

see Respirology, R12

Etiology
- 1 per 3,000 live births, mostly Caucasians
- autosomal recessive, CFTR gene found on chromosome 7 (ΔF508 mutation in 70%, but >1,600 different mutations identified) resulting in a dysfunctional chloride channel on the apical membrane of cells
- leads to relative dehydration of airway secretions, resulting in impaired mucociliary transport and airway obstruction

Clinical Presentation
- neonatal: meconium ileus, prolonged jaundice, antenatal bowel perforation
- infancy: pancreatic insufficiency with steatorrhea and FTT (despite voracious appetite), anemia, hypoproteinemia, hypotension, hypochloremic metabolic alkalosis and hypotonic dehydration
- childhood: heat intolerance, wheezing or chronic cough, recurrent chest infections (S. aureus, P. aeruginosa, H. influenzae), hemoptysis, nasal polyps, distal intestinal obstruction syndrome, rectal prolapse, clubbing of fingers
- older patients: COPD, infertility (males), decreased fertility (female)

Investigations
- sweat chloride test x 2 (>60 mEq/L)
  - false positive tests: malnutrition, atopic dermatitis, hypothyroidism, hypoparathyroidism, GSD, adrenal insufficiency, G6PD, Klinefelter syndrome, technical issues, autonomic dysfunction, familial cholestasis syndrome
  - false negative tests: technical problem with test, malnutrition, skin edema, mineralocorticoids

Management
- nutritional counselling: high calorie diet, pancreatic enzyme replacements, fat soluble vitamin supplements
- management of chest disease: physiotherapy, postural drainage, exercise, bronchodilators, aerosolized DNase and inhaled hypertonic saline, antibiotics (e.g. cephalosporin, clavulanic acid, ciprofloxacin, inhaled tobramycin depending on sputum C&S), lung transplantation
- genetic counselling

Complications
- respiratory failure, pneumothorax (poor prognostic sign), cor pulmonale (late), pancreatic fibrosis with DM, gallstones, cirrhosis with portal HTN, infertility (male)
- early death (current median survival in Canada is 46.6 yr)
# Evaluation of Limb Pain

## Table 46. Differential Diagnosis of Limb Pain

<table>
<thead>
<tr>
<th>Cause</th>
<th>&lt;3 yr</th>
<th>3-10 yr</th>
<th>&gt;10 yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trauma</strong></td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Infectious</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Septic arthritis</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Osteomyelitis</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Transient synovitis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>JIA</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>SLE</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>HSP</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td><strong>Anatomic/Orthopedic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Legg-Calvé-Perthes disease</td>
<td>x</td>
<td>x</td>
<td></td>
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<tr>
<td>Slipped capital femoral epiphysis</td>
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<td>x</td>
<td></td>
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<tr>
<td>Osgood-Schlatter disease</td>
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<tr>
<td><strong>Neoplastic</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Bone tumour</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hemophilia (hemarthrosis)</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Sickle cell anemia</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td><strong>Pain Syndromes</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Growing pains</td>
<td>x</td>
<td>x</td>
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</tr>
<tr>
<td>Fibromyalgia</td>
<td>x</td>
<td>x</td>
<td></td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
<td>x</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- must rule out infection, malignancy, and acute orthopedic conditions

## History
- demographics (age, gender)
- pattern of onset and progression of symptoms (including acuity and chronicity)
- morning stiffness, limp/weight-bearing status, night pain
- joint involvement (type, distribution) + spine (axial) involvement
- extra-articular manifestations and systemic symptoms
- functional status – activities of daily living
- family history (arthritis, IBD, psoriasis, spondyloarthopathies, uveitis, bleeding disorders, sickle cell anemia)
- past medical illness, intercurrent infection, travel, sick contact history, joint injury

## Physical Exam
- growth parameters
- screening examination (pediatric gait, arms, legs, spine exam)
- joint exam: inspection/palpation (swelling, erythema, warmth, tenderness, deformity), ROM
- adjacent structures (bone, tendon, muscle, skin)
- leg length
- neurologic exam

## Investigations
- basic: CBC and differential, blood smear, ESR, CRP, x-ray
- as indicated: blood (ANA, RF, culture, viral/bacterial serology, CK, PTT, sickle cell screen, immunoglobulins, complement), urinalysis, synovial fluid (cell count, Gram stain, culture), TB skin test, imaging, bone marrow aspiration, slit lamp exam

**Red Flags for Limb Pain**
- Fever, pinpoint pain/tenderness, pain out of proportion to degree of inflammation, night pain, weight loss, erythema
Growing Pains

**Epidemiology**
- age 2-12 yr, M=F

**Clinical Presentation**
- diagnosis of exclusion
- intermittent, non-articular pain in childhood with normal physical exam findings
- pain at night, often bilateral and limited to the calf, shin, or thigh; typically short-lived
- relieved by heat, massage, mild analgesics
- child is well, asymptomatic during the day, no functional limitation
- possible family history of growing pains

**Management**
- lab investigations not necessary if typical presentation; reassurance and supportive management

Transient Synovitis of the Hip

- benign, self-limited disorder, usually occurs after URTI, pharyngitis, AOM

**Epidemiology**
- age 3-10 yr, M>F

**Clinical Presentation**
- afebrile or low-grade fever, pain typically occurs in hips, knees (referred from hip); painful limp but full ROM (pain not as pronounced as in joint or bone infections)
- symptoms resolve over 7-10 d

**Investigations**
- WBC within normal limits; ESR and CRP may be mildly elevated
- joint effusions may be seen on imaging
- diagnosis of exclusion (rule out septic arthritis and osteomyelitis)

**Treatment**
- symptomatic and anti-inflammatory medications

Septic Arthritis and Osteomyelitis

- MEDICAL EMERGENCY
- see Orthopedics, OR10

<table>
<thead>
<tr>
<th>Age</th>
<th>Pathogens</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>GBS, S. aureus, Gram negative bacilli</td>
<td>cloxacillin + aminoglycoside or cefotaxime</td>
</tr>
<tr>
<td>Infant (1-3 mo)</td>
<td>Strept. spp., Staph. spp., H. influenzae Pathogens as per neonate</td>
<td>cloxacillin + cefotaxime</td>
</tr>
<tr>
<td>Child</td>
<td>S. aureus, S. pneumoniae, GAS</td>
<td>cefazolin</td>
</tr>
<tr>
<td>Adolescent</td>
<td>As above; also N. gonorrhoeae</td>
<td>cefazolin</td>
</tr>
<tr>
<td>Sickle cell disease</td>
<td>As above; also Salmonella</td>
<td>cefotaxime</td>
</tr>
</tbody>
</table>

GAS = group A Strep; GBS = group B Strep  Adapted from Tse SML, Laxer RM. Pediatrics in Review 2006;27:170-179

Juvenile Idiopathic Arthritis

- a heterogenous group of conditions characterized by persistent arthritis in children <16 yr
- diagnosis: arthritis in ≥1 joint(s); duration ≥6 wk; onset age <16 yr old; exclusion of other causes of arthritis; classification defined by features/number of joints affected in the first 6 mo of onset

Systemic Arthritis (Still’s Disease)
- onset at any age, M=F
- once or twice daily fever spikes (≥38.5°C) ≥2 d/wk; children usually acutely unwell during fever episodes
- extra-articular features: erythematous “salmon-coloured” maculopapular rash, lymphadenopathy, hepatosplenomegaly, leukocytosis, thrombocytosis, anemia, serositis
• arthritis may occur weeks to months later
• high ESR, CRP, WBC, platelet count

Oligoarticular Arthritis (1-4 joints)
• onset early childhood, F>M
• persistent: affects no more than 4 joints during the disease course
• extended: affects more than 4 joints after the first 6 mo
• typically affects large joints: knees > ankles, elbows, wrists; hip involvement unusual
• ANA positive ~60-80%, RF negative
• screening eye exams for asymptomatic anterior uveitis (occurs in ~30%)
• complications: knee flexion contracture, quadriceps atrophy, leg-length discrepancy, growth disturbances

Polyarticular Arthritis (5 or more joints)
• RF negative
  ▪ onset: 2-4 yr and 6-12 yr, F>M
  ▪ symmetrical involvement of large and small joints of hands and feet, TMJ, cervical spine
• RF positive
  ▪ onset: late childhood/early adolescence, F>M
  ▪ similar to the aggressive form of adult rheumatoid arthritis
  ▪ severe, rapidly destructive, symmetrical arthritis of large and small joints
  ▪ may have rheumatoid nodules at pressure points (elbows, knees)
  ▪ unremitting disease, persists into adulthood

Enthesitis-Related Arthritis
• onset: late childhood/adolescence, M>F
• arthritis and/or enthesitis (inflammation at the site where tendons or ligaments attach to the bone)
• weight bearing joints, especially hip and intertarsal joints
• risk of developing ankylosing spondylitis in adulthood

Psoriatic Arthritis
• onset: 2-4 yr and 9-11 yr, F>M
• arthritis and psoriasis OR arthritis and at least two of:
  ▪ dactylitis, nail pitting or other abnormalities, or family history of psoriasis in a 1st degree relative
  ▪ asymmetric or symmetric small or large joint involvement

Management
• goals of therapy: eliminate inflammation, prevent joint damage, promote normal growth and development as well as normal function, minimize medication toxicity
• exercise to maintain ROM and muscle strength
• multidisciplinary approach: OT/PT, social work, orthopedics, ophthalmology, rheumatology
• 1st line drug therapy: NSAIDs, intra-articular corticosteroids
• 2nd line drug therapy: DMARDs (methotrexate, sulfasalazine, leflunamide), corticosteroids (acute management of severe arthritis, systemic symptoms of JIA, topical eye drops for uveitis), biologic agents

Reactive Arthritis
• see Rheumatology, RH24
• arthritis (typically the knee) follows bacterial infection, especially with Salmonella, Shigella, Yersinia, Campylobacter, Chlamydia, and most commonly Streptococcus (post-streptococcal reactive arthritis)
• typically resolves spontaneously
• may progress to chronic illness or Reiter’s syndrome (urethritis, conjunctivitis)

Lyme Arthritis
• see Infectious Diseases, ID23
• caused by spirochete Borrelia burgdorferi
• incidence highest among 5-10 yr olds
• do not treat children <8 yr old with doxycycline (may cause permanent tooth discoloration)
Systemic Lupus Erythematosus

- see Rheumatology, RH11
- autoimmune illness affecting multiple organ systems
- incidence 1/1,000, more commonly age >10, F:M = 10:1
- childhood-onset SLE vs. adult-onset SLE: children have more active disease, are more likely to have renal disease, and children receive more intensive drug therapy and have a poorer prognosis

Vasculitides

HENOPH-SCHÖNLEIN PURPURA
- most common vasculitis of childhood, peak incidence 4-10 yr, M:F = 2:1
- vasculitis of small vessels
- often have history of URTI 1-3 wk before onset of symptoms

Clinical Presentation
- clinical tetrad: 1) palpatble purpura, 2) abdominal pain, 3) arthritis
- skin: palpatble, non-thrombocytopenic purpura in lower extremities and buttocks, edema, scrotal swelling
- joints: arthritis/arthralgia involving large joints associated with painful edema
- GI: abdominal pain, GI bleeding, intussusception
- renal: microscopic hematuria, IgA nephropathy, proteinuria, HTN, renal failure in <5%

Management
- mainly supportive
- anti-inflammatory medications for joint pain, corticosteroids for select patients
- monitor for protein on urinalysis every month for 6 mo, checking for renal disease, which may develop late (immunosuppressive therapy if severe)

Prognosis
- self-limited, resolves within 4 wk
- recurrence in about one-third of patients
- long-term prognosis dependent on severity of nephritis

KAWASAKI DISEASE
- acute vasculitis of unknown etiology (likely triggered by infection)
- medium-sized vasculitis with predilection for coronary arteries
- most common cause of acquired heart disease in children in developed countries
- peak age: 3 mo-5 yr; Asians > Blacks > Caucasians

Diagnostic Criteria
- fever persisting ≥5 d AND ≥4 of the following features
  1. bilateral, non-exudative conjunctival injection
  2. oral mucous membrane changes (fissured lips, strawberry tongue, injected pharynx)
  3. changes of the peripheral extremities
     - acute phase: extremity changes including edema of hands and feet or erythema of palms or soles
     - subacute phase: periungual desquamation
  4. polymorphous rash
  5. cervical lymphadenopathy >1.5 cm in diameter (usually unilateral)
- exclusion of other diseases (e.g. scarlet fever, measles)
- atypical Kawasaki disease: fever persisting ≥5 d and 2-3 of the above criteria
- further evaluation dictated by CRP, ESR, and supplemental laboratory criteria

Management
- initial therapy: IVIG (2g/kg) and high (anti-inflammatory) dose of ASA
- once afibrile >48 hours: low (anti-platelet) dose of ASA until platelets normalize, or longer if coronary artery involvement
- IVIg within 10 d of onset reduces risk of coronary aneurysm formation
- baseline 2D-Echo and follow up periodic 2D-Echo (usually at 2, 6 wk)

Complications
- coronary artery vasculitis with aneurysm formation occurs in 20-25% of untreated children,
  <5% if receive IVIg within 10 d of fever
- 50% of aneurysms regress within 2 yr
- anticoagulation for multiple or large coronary aneurysms
- risk factors for coronary disease: male, age <1 or >9 yr, fever >10 d, Asian or Hispanic ethnicity, thrombocytopenia, hyponatremia

Diagnostic Criteria for Kawasaki Disease

| Warm CREAM | Fever ≥5 d with ≥4 of:
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjunctivitis</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td></td>
</tr>
<tr>
<td>Edema/Erythema (hands and feet)</td>
<td></td>
</tr>
<tr>
<td>Adenopathy</td>
<td></td>
</tr>
<tr>
<td>Mucosal involvement</td>
<td></td>
</tr>
</tbody>
</table>
## Common Medications

### Table 48. Commonly Used Medications in Pediatrics

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Indications</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>acetaminophen (Tylenol®)</td>
<td>Analgesic, antipyretic</td>
<td>Not to exceed 60 mg/kg/d in neonates or 75 mg/kg/d in older children to a max of 4 g/d Causes hepatotoxicity at high doses</td>
</tr>
<tr>
<td>amoxicillin (Amoxicil®)</td>
<td>Otitis media</td>
<td></td>
</tr>
<tr>
<td>dexamethasone</td>
<td>Croup Acute asthma</td>
<td></td>
</tr>
<tr>
<td>fluticasone (Flovent®)</td>
<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>ibuprofen (Advil®)</td>
<td>Analgesic, antipyretic</td>
<td>Cautious use in patients with liver impairment, history of GI bleeding or ulcers</td>
</tr>
<tr>
<td>iron</td>
<td>Anemia</td>
<td>SE: dark stool, constipation, dark urine</td>
</tr>
<tr>
<td>omeprazole</td>
<td>GERO</td>
<td>SE: headache, diarrhea, nausea, abdominal pain</td>
</tr>
<tr>
<td>ondansetron</td>
<td>Post-operative N/V Gastroenteritis Cyclic vomiting</td>
<td>SE: QTc prolongation, orally disintegrating tablets contain phenylalanine (caution in PKU patients)</td>
</tr>
<tr>
<td>fenobarbital</td>
<td>Seizures</td>
<td>SE: CNS depression</td>
</tr>
<tr>
<td>polyethylene glycol 3350 (PEG)</td>
<td>Disimpaction: 1-1.5 g/kg/d x 3 d Maintenance: starting dose at 0.4-1 g/kg</td>
<td></td>
</tr>
<tr>
<td>prednisone/prednisolone</td>
<td>Asthma</td>
<td>Oral prednisone is bitter tasting, consider using prednisolone</td>
</tr>
<tr>
<td>salbutamol (Ventolin®)</td>
<td>Acute asthma</td>
<td>Can cause tachycardia, hypokalemia, restlessness</td>
</tr>
</tbody>
</table>

**Source:** Lau E. (2009) The 2010-2011 Formulary – The Hospital for Sick Children
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<th>Full Form</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABI</td>
<td>ankle-brachial index</td>
<td></td>
</tr>
<tr>
<td>ABG</td>
<td>arterial blood gas</td>
<td></td>
</tr>
<tr>
<td>APL</td>
<td>abductor pollicis longus</td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>acute respiratory distress syndrome</td>
<td></td>
</tr>
<tr>
<td>ATLS</td>
<td>advanced trauma life support</td>
<td></td>
</tr>
<tr>
<td>BMR</td>
<td>basal metabolic rate</td>
<td></td>
</tr>
<tr>
<td>CHF</td>
<td>congestive heart failure</td>
<td></td>
</tr>
<tr>
<td>CMC</td>
<td>carpo-metacarpal</td>
<td></td>
</tr>
<tr>
<td>CO</td>
<td>carbon monoxide</td>
<td></td>
</tr>
<tr>
<td>CSF</td>
<td>cerebrospinal fluid</td>
<td></td>
</tr>
<tr>
<td>CVD</td>
<td>cerebrovascular disease</td>
<td></td>
</tr>
<tr>
<td>CCR</td>
<td>chest x-ray</td>
<td></td>
</tr>
<tr>
<td>D5W</td>
<td>5% dextrose in water</td>
<td></td>
</tr>
<tr>
<td>DIEP</td>
<td>deep inferior epigastric perforator</td>
<td></td>
</tr>
<tr>
<td>DIP</td>
<td>distal interphalangeal joint</td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>ENT</td>
<td>ear, nose, throat</td>
<td></td>
</tr>
<tr>
<td>EOM</td>
<td>extraocular movement</td>
<td></td>
</tr>
<tr>
<td>EPB</td>
<td>extensor pollicis brevis</td>
<td></td>
</tr>
<tr>
<td>FDP</td>
<td>flexor digitorum profundus</td>
<td></td>
</tr>
<tr>
<td>FDS</td>
<td>flexor digitorum superficialis</td>
<td></td>
</tr>
<tr>
<td>FTSG</td>
<td>full thickness skin graft</td>
<td></td>
</tr>
<tr>
<td>GBS</td>
<td>group B Streptococcus</td>
<td></td>
</tr>
<tr>
<td>HTN</td>
<td>hypertension</td>
<td></td>
</tr>
<tr>
<td>I&amp;I</td>
<td>incision and drainage</td>
<td></td>
</tr>
<tr>
<td>ICP</td>
<td>intracranial pressure</td>
<td></td>
</tr>
<tr>
<td>ICCU</td>
<td>intensive care unit</td>
<td></td>
</tr>
<tr>
<td>IGAP</td>
<td>inferior gluteal artery perforator</td>
<td></td>
</tr>
<tr>
<td>IP</td>
<td>interphalangeal</td>
<td></td>
</tr>
<tr>
<td>IVIg</td>
<td>intravenous immunoglobulin</td>
<td></td>
</tr>
<tr>
<td>MC</td>
<td>metacarpal</td>
<td></td>
</tr>
<tr>
<td>MCP</td>
<td>metacarpal phalangeal joint</td>
<td></td>
</tr>
<tr>
<td>NS</td>
<td>normal saline</td>
<td></td>
</tr>
<tr>
<td>NSAIDs</td>
<td>nonsteroidal anti-inflammatory drugs</td>
<td></td>
</tr>
<tr>
<td>OM</td>
<td>otitis media</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>operating room</td>
<td></td>
</tr>
<tr>
<td>ORIF</td>
<td>open reduction internal fixation</td>
<td></td>
</tr>
<tr>
<td>PIP</td>
<td>proximal interphalangeal joint</td>
<td></td>
</tr>
<tr>
<td>PMN</td>
<td>polymorphonuclear</td>
<td></td>
</tr>
<tr>
<td>PVD</td>
<td>peripheral vascular disease</td>
<td></td>
</tr>
<tr>
<td>RA</td>
<td>rheumatoid arthritis</td>
<td></td>
</tr>
<tr>
<td>RL</td>
<td>Ringer's lactate</td>
<td></td>
</tr>
<tr>
<td>ROM</td>
<td>range of motion</td>
<td></td>
</tr>
<tr>
<td>SGAP</td>
<td>superior gluteal artery perforator</td>
<td></td>
</tr>
<tr>
<td>SIADH</td>
<td>syndrome of inappropriate antidiuretic hormone</td>
<td></td>
</tr>
<tr>
<td>SIEA</td>
<td>superficial inferior epigastric artery</td>
<td></td>
</tr>
<tr>
<td>SLT</td>
<td>speech language pathology</td>
<td></td>
</tr>
<tr>
<td>SSS</td>
<td>superior orbital fissure</td>
<td></td>
</tr>
<tr>
<td>STSG</td>
<td>split thickness skin graft</td>
<td></td>
</tr>
<tr>
<td>TBSA</td>
<td>total body surface area</td>
<td></td>
</tr>
<tr>
<td>TMJ</td>
<td>temporomandibular joint</td>
<td></td>
</tr>
<tr>
<td>UCL</td>
<td>ulnar collateral ligament</td>
<td></td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet</td>
<td></td>
</tr>
</tbody>
</table>

### Basic Anatomy Review

#### Skin

- **Skin Layers**
  - **Epidermis**
  - **Dermis**
  - **Subcutaneous tissue**

- **Skin Grafts**
  - **Split thickness skin graft**
  - **Full thickness skin graft**

#### Hand

**BONES AND NERVES**

1. Radius
2. Scaphoid
3. Trapezium
4. Trapezoid
5. Capitate
6. Ulna
7. Lunate
8. Pisiform
9. Triquetrum
10. Hamate
11. Metacarpal bones

**Arterial Supply in the Hand**

- **Radial**
- **Ulnar**
- **Median**

**Sensory Distribution in the Hand**

- **Hand Bones**
  - **Carpal Bones**
  - **Metacarpal Bones**

**Arterial Supply**

- **A:** Superficial palmar arch
- **B:** Deep palmar arch
- **C:** Ulnar artery
- **D:** Radial artery

---

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© Times-McCraw 2003

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TENDONS

Figure 5. Flexor tendon insertion at PIP and DIP

Figure 6. Extensor mechanism of digits

Figure 7. Carpal tunnel

Figure 8. Extensor compartments of the wrist (dorsal view and cross-sectional view)

Flexor Tendons
All require OR repair

Extensor Tendons
ER repair unless proximal/multiple tendons

Carpal Bone Mnemonic
So Scaphoid
Long Lunate
To Triquetrum
Pinky Pisiform
Here Hamate
Comes Capitate
The Trapezoid
Thumb Trapezium

1. Extensor retinaculum
Compartments
2. Abductor pollicis longus
3. Extensor pollicis brevis

Compartments
4. Extensor carpi radialis brevis
5. Extensor carpi radialis longus

Compartments
6. Extensor pollicis longus
7. Extensor digitorum
8. Extensor indicis

Compartments
9. Extensor digit minimi

Compartments
10. Extensor carpi ulnaris

Distal interphalangeal joint
Flexor digitorum profundus
Proximal interphalangeal joint
Camper’s chiasm
Flexor digitorum superficialis
Metacarpal phalangeal joint
Lateral bands
Central slip
DIP
PIP
MCP
Extensor hood
Oblique fibres
Sagittal fibres
Lumbrical
Interosseous muscles
Extensor digitorum communis

Distal phalanx
9. Extensor tendon
10. Flexor tendon

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Nail anatomy
Brachial Plexus

Figure 9. Brachial plexus anatomy

Face

Figure 10. Skull and facial bones
Skin Lesions and Masses

Differential Diagnosis of Skin Lesions/Masses

- for background information and medical management (see Dermatology, D5)
- for biopsy techniques, see Skin Biopsy Types and Techniques, PL7

Surgical Management of Malignant Skin Lesions

- surgical treatment for all malignant skin lesions involve total excision of the primary lesion
- excision margin of lesion depends on the type of lesion, the lesion diameter and (for melanoma) the lesion depth
- for decisions regarding reconstruction using flaps or skin grafts, see Reconstruction, PL11

Precursors of Malignant Lesions

Table 1. Precursors

<table>
<thead>
<tr>
<th>Precursor</th>
<th>Basal Cell Carcinoma</th>
<th>Squamous Cell Carcinoma</th>
<th>Malignant Melanoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevus sebaceous of Jadassohn</td>
<td>Actinic keratosis</td>
<td>Bowen's disease</td>
<td>Atypical mole</td>
</tr>
<tr>
<td></td>
<td>Bowenoid papulosis</td>
<td>Paget’s disease</td>
<td>Lentigo maligna</td>
</tr>
<tr>
<td></td>
<td>Lentigo maligna</td>
<td></td>
<td>Giant congenital nevus</td>
</tr>
</tbody>
</table>

Surgical Margins

Table 2. Surgical Margins for Basal Cell Carcinoma

<table>
<thead>
<tr>
<th>Type of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk (&lt;20 mm trunk; &lt; 6 mm face, hands, feet)</td>
<td>4 mm</td>
</tr>
<tr>
<td>High Risk (&gt;20 mm trunk; &gt;6 mm face, hands, feet)</td>
<td>10 mm</td>
</tr>
</tbody>
</table>

Table 3. Surgical Margins for Squamous Cell Carcinoma

<table>
<thead>
<tr>
<th>Diameter or Location of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2 cm*</td>
<td>4 mm*</td>
</tr>
<tr>
<td>&gt;2 cm</td>
<td>6 mm</td>
</tr>
<tr>
<td>High risk (facial)</td>
<td>6 mm</td>
</tr>
<tr>
<td>Low risk (elsewhere)</td>
<td>4 mm</td>
</tr>
</tbody>
</table>

*For a high risk lesion that is <2 cm in diameter, use a 6 mm margin
Table 4. Surgical Margins for Malignant Melanoma

<table>
<thead>
<tr>
<th>Depth of Lesion</th>
<th>Surgical Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td>In situ</td>
<td>0.5 cm</td>
</tr>
<tr>
<td>&lt;1 mm</td>
<td>1 cm</td>
</tr>
<tr>
<td>1.01-1.99 mm</td>
<td>1-2 cm</td>
</tr>
<tr>
<td>≥2 mm</td>
<td>At least 2 cm</td>
</tr>
</tbody>
</table>

**Surgical Techniques**

**Sutures and Suturing**

**ANESTHESIA**
- irrigate before injecting anesthetic, followed by debridement

**Table 5. Toxic Limit and Duration of Action (1 cc of 1% solution contains 10 mg lidocaine)**

<table>
<thead>
<tr>
<th>Without Epinephrine</th>
<th>With Epinephrine (vasoconstrictor, limits bleeding)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lidocaine (Xylocaine[^a])</td>
<td>5 mg/kg, lasts 45-60 min</td>
</tr>
<tr>
<td>Bupivicaine (Marcaine[^c]) for longer analgesic effect</td>
<td>2 mg/kg, lasts 2-4 h</td>
</tr>
</tbody>
</table>

- example: if you have a 70 kg patient, the toxic limit for 1% lidocaine without epinephrine is
  - 5 mg x 70 kg = 350 mg TOXIC LIMIT
  - 350 mg ÷ 10 mg/cc = 35 cc MAX BOLUS INJECTION of 1% lidocaine without epinephrine (may add more after 30 min)

**IRRIGATION AND DEBRIDEMENT**
- irrigate copiously with a physiologic solution such as Ringer’s lactate or normal saline to remove surface clots, foreign material, and bacteria
- use a 19 gauge needle and 35 cc syringe to generate ~18 psi when irrigating (~8 psi will reach the wound)
- debride all obviously devitalized tissue, irregular or ragged wounds must be excised to produce sharp wound edges that will assist healing when approximated
- wounds left unapproximated ≥8 h should be debrided to ensure wound edges are optimized for healing

**SUTURES**
- use of a particular suture material is highly dependent on surgeon preference; however, skin should be closed with a non absorbable material when traumatic mechanisms are involved
- suture materials are divided into absorbable vs. non-absorbable and monofilament vs. braided

**Table 6. Suture Materials: Absorbable vs. Non-absorbable and Monofilament vs. Multifilament**

<table>
<thead>
<tr>
<th>Suture Materials</th>
<th>Uses</th>
<th>Examples</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absorbable</td>
<td>Deep sutures under short-term tension</td>
<td>Plain gut[^a], Vicryl[^a], Polysorb[^a]</td>
<td>loses at least 50% of their strength in 4 wk; eventually absorbed</td>
</tr>
<tr>
<td></td>
<td>Skin closure in children</td>
<td>Nylon, polypropylene (Prolene), stainless steel</td>
<td>Lower likelihood of wound dehiscence, more difficult to tie</td>
</tr>
<tr>
<td>Non-absorbable</td>
<td>Sites of long-term tension</td>
<td>Monosof[^a], Monocryl[^a], Biosyn[^a]</td>
<td>Slides through tissue with less friction; more memory/stiffness</td>
</tr>
<tr>
<td>Monofilament</td>
<td>Everyday use and optimal for contaminated and infected wounds (lower likelihood of bacterial trapping in suture material)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multifilament</td>
<td>AVOID in contaminated wounds (increased likelihood of bacterial trapping)</td>
<td>Vicryl[^a] and Silk</td>
<td>Less memory/stiffness thus easier to work with</td>
</tr>
</tbody>
</table>

**Basic Suturing Techniques**

**Basic Suture Methods**
- simple interrupted: can be used in almost all situations
- sub-cuticular: good cosmetic result but weak, used in combination with deep sutures; not used in trauma
- vertical mattress: for areas difficult to evert (e.g. dorsum of the hand)
- horizontal mattress: evertng, time saving
- continuous over and over (i.e. “running”, “baseball stitch”): time saving, good for hemostasis

**Basic Principles**
- minimize tissue trauma: follow curve of needle, insert and exit at 90 degrees to the wound edge, handle wound edges gently (use toothed forceps), use just enough tension to approximate edges (do not strangulate)
- use appropriate needles and sutures
- ensure good cosmesis

---

[^a]: Baseer Khan, Tabby Lulham 2010

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© Baseer Khan, Tabby Lulham 2010
Other Skin Closure Materials
- tapes: may be indicated for superficial wounds and those with opposable edges. Tape cannot be used on actively bleeding wounds. When placed across the incision, will prevent surface marks and can be used primarily or after surface sutures have been removed. Tape burns may occur if there is excessive tension or swelling around the incision
- skin adhesives: e.g. 2-octylcyanoacrylate (e.g. Dermabond®) works well on small areas without much tension or shearing; may cause irreversible tattooing
- staples: steel-titanium alloys that incite minimal tissue reaction (healing is comparable to wounds closed by suture)

Excision
- plan your incision along relaxed skin tension lines to minimize appearance of scar
- use elliptical incision to prevent "dog ears" (heaped up skin at end of incision) so the length of the ellipse should be approximately 3x the width
- if needed, undermine skin edges to decrease wound tension
- use layered closure including dermal sutures when wound is deeper than superficial (decreases tension)

Skin Biopsy Types and Techniques
SHAVE BIOPSY
- used for superficial lesions where sampling of the full thickness of the dermis is not necessary or practical
- most suitable lesions for shave biopsies are either elevated above the skin or have pathology confined to the epidermis (e.g. seborrheic or actinic keratoses, skin tags, warts, and superficial basal cell or squamous cell carcinomas)
- rapid, requires little training, and does not require sutures for closure
- will leave a circular scar
- can leave an indented scar
- heals by secondary intent (moist dressings should be used)
- should not be used for pigmented lesions – an unsuspected melanoma cannot be properly staged if partially removed

INCISIONAL BIOPSY
- can either be a punch biopsy or can be an ellipse including the lesion
- gives pathologists a portion of the lesion and the border with normal skin too

PUNCH BIOPSY
- involves the removal of a core-shaped piece of tissue, performed with round, disposable knives ranging in diameter from 2-10 mm
- allows sampling of the deep dermis
- can be used for the diagnosis and treatment of small pigmented lesions and atypical moles
- punch biopsy wounds can be closed with suture or left to heal by secondary intention. Punches greater than 3 mm may produce scarring and are best closed with one or two sutures
- has low incidence of infection, bleeding, nonhealing, significant scarring

EXCISIONAL BIOPSY
- performed for lesions that require complete removal for diagnostic or therapeutic purposes
- performed for lesions that cannot be adequately punch biopsied due to size, depth, or location
- requires the greatest amount of expertise and time
- always requires sutures for closure

TECHNIQUE
General
- all biopsies performed in clinic are done using aseptic technique, but are not sterile
- sterile gloves are indicated for biopsies and excisions in all patients

Preparing the Site
- common skin antisepsics (betadine, chlorhexidine) can be used to prepare the biopsy site
- chlorhexidine is used in concentrations ranging from 0.5-4%. This higher concentration cannot be used on the face as it could get into the eyes or ears and may burn or cause damage. Most chlorhexidine preps also contain alcohol which can be flammable, so allow to dry before the biopsy and certainly before using any cautery
- mark the intended lesion and surgical margins with a surgical marker since they may be temporarily obliterated following injection of the anesthetic
- for all biopsies, a sterile drape technique is indicated. A fenestrated surgical drape is placed around the biopsy site after the area is cleansed and anesthetized

Anesthesia
- most commonly used local anesthetic is 1% or 2% lidocaine (with epinephrine)
- small amounts of epinephrine are added to constrict blood vessels, decrease bleeding, prolong anesthesia, and limit lidocaine toxicity. The local with epinephrine can be injected directly into the lesion
• local anesthetics with epinephrine may be used anywhere in the body (including the digits – except if the digits have been significantly injured and could have vascular compromise – e.g. saw injury)
• epinephrine should be avoided in patients with history of vascular compromise
• a field block should be performed for larger lesions by placing a ring of anesthetic around the surgical site, advancing and injecting through a site that has been previously anesthetized

## Wounds

### Causal Conditions

- laceration: cut or torn tissue
- abrasion: superficial skin layer is removed, variable depth
- contusion: injury caused by forceful blow to the skin and soft tissue; entire outer layer of skin intact yet injured
- avulsion: tissue/limb forcefully separated from surrounding tissue, either partially or fully; “de-gloving”
- puncture wounds: cutaneous opening relatively small as compared with depth (e.g. needle)
  - includes bite wounds
- crush injuries: caused by compression
- thermal and chemical wounds

### Principles of Wound Healing

• wound: disruption of the normal anatomical relationships of tissue as a result of injury

#### FACTORS INFLUENCING WOUND HEALING

<table>
<thead>
<tr>
<th>Local (reversible/controllable)</th>
<th>General (often irreversible)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mechanical (local trauma, tension)</td>
<td>age</td>
</tr>
<tr>
<td>blood supply (ischemia/circulation)</td>
<td>nutrition (protein, vitamin C, O₂)</td>
</tr>
<tr>
<td>temperature</td>
<td>smoking</td>
</tr>
<tr>
<td>technique and suture materials</td>
<td>chronic illness (e.g. DM, cancer, CVD)</td>
</tr>
<tr>
<td>retained foreign body</td>
<td>immunosuppression (steroids, chemo, radiation)</td>
</tr>
<tr>
<td>infection</td>
<td>collagen vascular disease</td>
</tr>
<tr>
<td>hematoma/seroma († infection rate)</td>
<td>tissue irradiation</td>
</tr>
<tr>
<td>venous HTN</td>
<td>peripheral vascular disease</td>
</tr>
<tr>
<td>PVD</td>
<td></td>
</tr>
</tbody>
</table>
ABNORMAL HEALING

Hypertrophic Scar
- scar remains roughly within boundaries of original scar
- red, raised, widened, frequently pruritic
- common sites: back, shoulder, sternum
- treatment: scar massage, pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision if other options fail (however, may still recur)

Keloid Scar
- scar grows outside boundaries of original scar
- red, raised, widened, frequently pruritic
- caused by 1. genetic factors, 2. endocrine factors and/or 3. excess tension on wound or delayed closure (as in burn wounds)
- common sites: back, shoulder, sternum, angle of mandible
- treatment: multimodal therapy, including pressure garments, silicone gel sheeting, corticosteroid injection, surgical excision with post-surgical management if other options fail (however, may still recur), fractional carbon dioxide ablative laser, radiation

Chronic Wound
- fails to achieve primary wound healing within 4-6 wk
- common chronic wounds include diabetic, pressure and venous stasis ulcers
- treatment: may heal with meticulous wound care; may also require surgical intervention
- Marjolin’s ulcer: squamous cell carcinoma arising in a chronic wound secondary to genetic changes caused by chronic inflammation → consider biopsy of chronic wound

WOUND HEALING

Primary (1st) Healing (First Intention)
- definition: wound closure by direct approximation of edges within hours of wound creation (i.e. with sutures, staples, skin graft, etc.)
- indication: recent (<6 h, longer with facial wounds), clean wounds
- contraindications: animal/human bites (except on face), crush injuries, infection, long time lapse since injury (>6-8 h), retained foreign body

Secondary (2nd) Healing/Spontaneous Healing (Second Intention)
- definition: wound left open to heal spontaneously (epithelialization 1 mm/d from wound margins in concentric pattern), contraction (myofibroblasts) and granulation – maintained in inflammatory phase until wound closed; requires dressing changes; inferior cosmetic result
- indication: when 1st closure not possible or indicated (see Primary Healing)

Tertiary (3rd) Healing/Delayed Primary Healing (Third Intention)
- definition: intentionally interrupt healing process (e.g. with packing), then wound can be closed at 4-10 d post-injury after granulation tissue has formed and there is <10^5 bacteria/gram of tissue
- indication: contaminated (high bacterial count), long time lapse since initial injury, severe crush component with significant tissue devitalization, closure of fasciotomy wounds
- prolongation of inflammatory phase decreases bacterial count and lessens chance of infection after closure

Contaminated and Infected Wounds

Definitions
- contamination: the presence of non-replicating microorganisms within a wound
- colonization: the presence of replicating microorganisms within a wound
- infection: greater than 10^6 microorganisms in a wound without intact epithelium, a wound may also be infected with small amounts of a very virulent organism (e.g. GBS)

Management of Acute Contaminated Wound (<24 h)
- cleanse and irrigate open wound with physiologic solution (NS or RL) using sufficient pressure
- evaluate for injury to underlying structures (vessels, nerve, tendon and bone)
- control active bleeding
- debridement: removal of foreign material, devitalized tissue, old blood
  - surgical debridement: blade and irrigation if indicated
- systemic antibiotics are commonly indicated for obvious infection. Risk factors include wound older than 8 h, severely contaminated, human/animal bites, immunocompromised, involvement of deeper structures (e.g. joints, fractures)
- ± tetanus toxoid 0.5 mL IM ± tetanus immunoglobulin 250 U deep IM (see Table 7 and Table 8)
• ± post-exposure treatment of
  • hepatitis B, HIV, hepatitis C (if titres confirmed at 6 mo)
• re-evaluate in 24-48 h for signs of superficial or deep infection
  • if evidence of infection, open infected portion of wound by removing sutures (i.e. erythema, warmth, pain, discharge), swab sample for culture and sensitivity, irrigate wound and allow healing secondary intention

Table 7. Risks for Tetanus

<table>
<thead>
<tr>
<th>Wound Characteristics</th>
<th>Tetanus-Prone</th>
<th>Not Tetanus-Prone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since injury</td>
<td>&gt;6 h</td>
<td>&lt;6 h</td>
</tr>
<tr>
<td>Depth of injury</td>
<td>&gt;1 cm</td>
<td>&lt;1 cm</td>
</tr>
<tr>
<td>Mechanism of Injury</td>
<td>Crush, burn, gunshot, frostbite, puncture through clothing, farming injury</td>
<td>Sharp cut (e.g. clean knife, clean glass)</td>
</tr>
<tr>
<td>Devitalized tissue</td>
<td>Present</td>
<td>Not present</td>
</tr>
<tr>
<td>Contamination (e.g. soil, dirt, saliva, grass)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Retained foreign body</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 8. Tetanus Immunization Recommendations

<table>
<thead>
<tr>
<th>History of Tetanus Immunization</th>
<th>Clean, Minor Wounds</th>
<th>All Other Wounds</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Td or Tdap*</td>
<td>Tig**</td>
</tr>
<tr>
<td>Uncertain or &lt;3 doses of immunization</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>3 doses received in immunization series</td>
<td>No~</td>
<td>No</td>
</tr>
</tbody>
</table>

  * 0.5 mL of combined tetanus and diptheria toxoids + acellular pertussis
  ** Tetanus immune globulin, 250 U given at a separate site from Td/Tdap

Management of Contaminated Wounds (>24 h, including ulcers)

• irrigation and debridement
• traumatic tattooing can occur if foreign materials left in wound
• systemic antibiotics indicated if there is concern of infection (e.g. redness, swelling, pain, clinically unwell)
• topical antimicrobials: beneficial for minor wounds, but no additional benefit for wounds requiring systemic antibiotics. May aid in healing of chronic wounds
• closure: final closure via secondary intention (most common), delayed wound closure (3º closure), skin graft or flap; successful closure depends on bacterial count of ≤10⁵/cm³ prior to closure and frequent dressing changes

BITES

• see Emergency Medicine, ER47

Dog and Cat Bites

• pathogens: Pasteurella multocida, S. aureus, S. viridans
• investigations: same as for human bites
• treatment: Clavulin® (500 mg PO q8h started immediately – amoxicillin + clavulanic acid)
  • ± rabies prophylaxis if animal has symptoms of rabies or unknown animal
  • ± rabies Ig (20 IU/kg around wound, or IM) and 1 of the 3 types of rabies vaccines (1.0 mL IM in deltoid, repeat on days 3, 7, 14, 28)
  • aggressive irrigation with debridement
  • healing by secondary intention is mainstay of treatment
  • only consider primary closure for bite wounds on the face; otherwise primary closure is contraindicated
  • contact Public Health if animal status unknown

Human Bites

• pathogens: Staphylococcus > α-hemolytic Streptococcus > Eikenella corrodens > Bacteroides
• mechanism: most commonly over dorsum of MCP from a punch in mouth; “fight-bite”
• serious, as mouth has 10⁹ microorganisms/mL, which get trapped in joint space when fist unclenches and overlying skin forms an air-tight covering ideal for anaerobic growth – can lead to septic arthritis
• investigations
  • radiographs prior to therapy to rule out foreign body (e.g. tooth) or fracture
  • culture for aerobic and anaerobic organisms, Gram stain
• treatment
  • urgent surgical exploration of joint, drainage and debridement of infected tissue
  • wound must be copiously irrigated
  • Clavulin® 500 mg PO q8h or (if penicillin allergy) clindamycin 300 mg PO q6h + ciprofloxacin 500 mg PO q12h + secondary closure
  • splint
**Dressings**

- there is no one dressing for any given type of wound. Dressing selection depends on the wound characteristics and surgeon preference
  - as the wound progresses through healing it will require different types of dressings, therefore, routine inspection is recommended
  - principles of dressings
    - moist vs. dry wounds
      - purpose of dressings should be to promote moist wound healing (i.e. moistening dry wounds or removing excess exudate/blood from wet wounds)
    - clean vs. infected wounds
      - clean wounds can be dressed with non-adherent dressing (which is non-adhering to epithelializing tissue); requires secondary dressing
      - infected wounds can be dressed with iodine gauze, silver-containing, or antimicrobial dressings
    - wide-based vs. cavitary/tunneling wounds
      - cavitary or tunnelling wounds (i.e. through a fascial layer) can be packed with saline-soaked (non-infected), betadine-soaked (infected) ribbon gauze, or other easily retrievable one-piece moisture providing dressing

**Table 9. Recommended Dressings for Wound Type**

<table>
<thead>
<tr>
<th>Wound Depth</th>
<th>Exudate Level</th>
<th>Dressing Material</th>
</tr>
</thead>
<tbody>
<tr>
<td>Superficial</td>
<td>Lightly exuding</td>
<td>Films (Opsite®, hydrogels (Intrasite®, Nu-gel®, Duoderm®))</td>
</tr>
<tr>
<td>Any exudate level</td>
<td></td>
<td>Contact layers</td>
</tr>
<tr>
<td>Superficial to Deep</td>
<td>Light to moderately exuding wounds</td>
<td>Amorphous gels, hydrogels, hydrocolloids (Duoderm®, Tegaderm®, collagen, hypertonic saline gauze (Mesalt®))</td>
</tr>
<tr>
<td></td>
<td>Moderately to heavily exuding wounds</td>
<td>Foams (Mepilex®, Allevyn®), alginates (Sorbsan®, Kaltostat®, hypertonic saline gauze, hydrofibre (Aquacel®))</td>
</tr>
</tbody>
</table>

Table adapted from Grabb & Smith’s Plastic Surgery, 6th ed. Chapter 3, Table 3.3

**Reconstruction**

**RECONSTRUCTION LADDER**

**Definition**
- an approach to wound management with successively more complex methods of treatment
- surgeons should start with the least complex method and progressively increase in complexity as appropriate

**SKIN GRAFTS**

**Definition**
- skin that is harvested from a donor site and transferred to the recipient site and that does not carry its own blood supply. Survival requires the generation of new blood vessels from the recipient site bed. They are classified according to the depth of dermis they contain: full thickness (entire epidermis + dermis) vs. split-thickness (epidermis + partial dermis)

**Donor Site Selection**
- must consider size, hair pattern, texture, thickness of skin, and colour (facial grafts best if taken from “blush zones” above clavicle e.g. pre/post auricular or neck)
- partial thickness grafts usually taken from inconspicuous areas (e.g. buttocks, lateral thighs, etc.)

**Partial Thickness Skin Graft Survival**
- 3 phases of skin graft “take”
  1. plasmatic imbibition: diffusion of nutrition from recipient site (first 48 h)
  2. inosculation: vessels in graft connect with those in recipient bed (day 2-3)
  3. neovascular ingrowth: graft revascularized (day 3-5)
- requirements for survival
  - bed: well-vascularized (unsuitable: bone, tendon, heavily irradiated, infected wounds, etc.)
  - contact between graft and recipient bed: fully immobile (decreased shearing and hematoma formation)
  - staples, sutures, splinting, and appropriate dressings (pressure) are used to prevent movement of graft and hematoma or seroma formation
  - site: low bacterial count (<10⁵/cm³, to prevent infection)
Classification of Skin Grafts

1. by species
   - autograft: from same individual
   - allograft (homograft): from same species, different individual
   - xenograft (heterograft): from different species (e.g. porcine)

2. by thickness: see Table 10

Table 10. Skin Grafts

<table>
<thead>
<tr>
<th></th>
<th>Split Thickness Skin Graft</th>
<th>Full Thickness Skin Graft</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Epidermis and part of dermis</td>
<td>Epidermis and all of dermis</td>
</tr>
<tr>
<td>Donor Site</td>
<td>More sites</td>
<td>Donor sites limited by the ability to use primary closure</td>
</tr>
<tr>
<td>Healing of Donor Site</td>
<td>Re-epithelialization via dermal appendages in graft and wound edges</td>
<td>Primary closure</td>
</tr>
<tr>
<td>Re-Harvesting</td>
<td>~10 d (faster on scalp)</td>
<td>N/A</td>
</tr>
<tr>
<td>Graft Take</td>
<td>More reliable and better survival; shorter nutrient diffusion distance</td>
<td>Lower rate of survival (thicker, slower vascularization)</td>
</tr>
<tr>
<td>Contraction*</td>
<td>Less 1st contraction, greater 2nd contraction (less with thicker graft)</td>
<td>Greater 1st contraction, less 2nd contraction</td>
</tr>
<tr>
<td>Aesthetic</td>
<td>Poor</td>
<td>Good</td>
</tr>
<tr>
<td>Comments</td>
<td>Can be meshed for greater area; Allows for extravasation of blood/serum</td>
<td>May use on face and fingers</td>
</tr>
<tr>
<td>Advantages</td>
<td>Takes well in less favourable conditions; Can cover a larger area</td>
<td>Resists contraction, better colour match; May use on face and fingers</td>
</tr>
<tr>
<td>Disadvantages</td>
<td>Contracts significantly, abnormal pigmentation, high susceptibility to trauma</td>
<td>Requires well vascularized bed; Must remove fat from graft before application</td>
</tr>
<tr>
<td>Uses</td>
<td>Large areas of skin, granulating tissue beds</td>
<td>Face (colour match), site where thick skin or decreased contraction is desired (e.g. finger)</td>
</tr>
</tbody>
</table>

*Primary: immediate reduction in size upon harvesting; Secondary: reduction in size once graft placed on wound bed

- mesh graft (split of full thickness skin graft)
  - advantages
    - prevents accumulation of fluids (e.g. hematoma, seroma)
    - covers a larger area
    - best for contaminated recipient site
  - disadvantages
    - poor cosmesis ("alligator hide" appearance)
    - has significant contraction

OTHER GRAFTS

Table 11. Various Tissue Grafts

<table>
<thead>
<tr>
<th>Graft Type</th>
<th>Use</th>
<th>Preferred Donor Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>Repair rigid defects</td>
<td>Cranial, rib, iliac, fibula</td>
</tr>
<tr>
<td>Cartilage</td>
<td>Restore contour of ear and nose</td>
<td>Ear, nasal septum, costal cartilage</td>
</tr>
<tr>
<td>Tendon</td>
<td>Repair damaged tendon</td>
<td>Palmaris longus, plantaris (present in 85% population)</td>
</tr>
<tr>
<td>Nerve</td>
<td>Conduit for regeneration across nerve gap</td>
<td>Sural, antebrachial cutaneous, medial brachial cutaneous</td>
</tr>
<tr>
<td>Vessel</td>
<td>Bridge vascular gaps</td>
<td>Forearm or foot vessels for small vessels, saphenous vein for larger vessels</td>
</tr>
<tr>
<td>Dermis</td>
<td>Contour restoration (+ fat for bulk)</td>
<td>Thick skin of buttock or abdomen</td>
</tr>
<tr>
<td>Fat</td>
<td>Contour restoration</td>
<td>Abdomen, any area with fat available</td>
</tr>
</tbody>
</table>

FLAPS

- definition: tissue transferred from one site to another with a known blood supply (random, pedicled or named); not dependent on neovascularization, unlike a graft
- may consist of: skin, subcutaneous tissue, fascia, muscle, bone, other tissue (e.g. omentum)
- classification: based on blood supply to skin (random, axial) and anatomic location (local, regional, distant)
- indications for flaps
  - replaces tissue loss due to trauma or surgery (reconstruction)
  - provides skin and temporary soft tissue coverage through which surgery can be carried out later
  - to aid healing or treatment of infection by providing vascularized tissue to a poorly vascularized bed
• **complications**: flap loss due to hematoma, seroma, infection, poor flap design, extrinsic compression (dressing too tight) or vascular failure/thrombosis, fat necrosis (in free and pedicled flaps)

**Random Pattern Flaps**
- blood supply by dermal and subdermal plexus to skin and subdermal tissue with random vascular supply
- limited length:width ratio to ensure adequate blood supply (typically 3:1)
- flap choice is often a combination of available tissue, type of tissue needed, location of reconstruction site with respect to donor site, and surgeon preference
- types
  - **rotation**: semicircular tissue rotated around a pivot point for defect closure; commonly used on sacral pressure sores
  - **transposition**: tissue is transposed around a pivot point from one location to another; commonly used on certain areas of the face using adjacent areas of excess skin laxity
  - **Z-plasty**: two triangular flaps are repositioned; used to reorient a scar, lengthen the line of a scar or to break up a scar
  - **advancement flaps** (V-Y, Y-V): defect is closed with unidirectional tissue advancement
    - single/bipedicle V-Y flaps: wounds with lax surrounding tissue; the pedicle is the deep tissue underlying the flap

**Axial Pattern Flaps (Arterialized)**
- flap contains a well-defined artery and vein
- allows greater length:width ratio (3-6:1)
- types
  - **peninsular flap**: skin and vessel intact in pedicle
  - **island flap**: vessel intact, pedicle is better defined
  - **free flap**: vascular supply anastomosed at recipient site by microsurgical techniques
- can be sub-classified according to tissue content of flap
  - e.g. musculocutaneous/myocutaneous (e.g. transverse rectus abdominal myocutaneous) vs. fasciocutaneous

**Free Flaps**
- transplanting expendable donor tissue from one part of the body to another by isolating and dividing a dominant artery and veins to a flap and performing a microsurgical anastomosis between these and the vessels in the recipient wound
- survival rates >95%
- types: muscle and skin (common), bone, jejunum, omentum, fascia
  - e.g. radial forearm, scapular, latissimus dorsi

---

**Figure 15. Wound care flaps – random pattern**

**Figure 16. Peninsular axial pattern flap**

**Figure 17. Island axial pattern flap**
### Table 12. Characteristics of Healthy Free Flaps

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Normal</th>
<th>Arterial Insufficiency</th>
<th>Venous Insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>Pink</td>
<td>Pale</td>
<td>Purple or blue</td>
</tr>
<tr>
<td>Temperature</td>
<td>Warm</td>
<td>Cool</td>
<td>Warm or cool</td>
</tr>
<tr>
<td>Arterial Pulse (Doppler)</td>
<td>+</td>
<td>–</td>
<td>±</td>
</tr>
<tr>
<td>Turgor</td>
<td>Soft, but with some firmness</td>
<td>Decreased tissue firmness</td>
<td>Increased (tissue firmness with tissue stiffness)</td>
</tr>
</tbody>
</table>

### Soft Tissue Infections

#### Table 13. Classification of Soft Tissue Infections by Depth

<table>
<thead>
<tr>
<th>Infection</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erysipelas</td>
<td>Superficial with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Cellulitis</td>
<td>Full thickness with subcutaneous tissue involvement</td>
</tr>
<tr>
<td>Fasciitis</td>
<td>Fascia</td>
</tr>
<tr>
<td>Myositis</td>
<td>Muscle</td>
</tr>
</tbody>
</table>

#### Erysipelas

**Definition**
- acute skin infection that is more superficial than cellulitis

**Etiology**
- typically caused by Group A β-hemolytic *Streptococcus*

**Clinical Features**
- intense erythema, induration, and **sharply demarcated borders** (differentiates it from other skin infections)

**Treatment**
- penicillin or first generation cephalosporin (e.g. cefazolin or cephalaxin)

#### Cellulitis

**Definition**
- non-suppurative infection of skin and subcutaneous tissues

**Etiology**
- skin flora most common organisms: *S. aureus*, β-hemolytic *Streptococcus*
- immunocompromised: Gram-negative rods and fungi

**Clinical Features**
- source of infection
  - trauma, recent surgery
  - PVD, DM – cracked skin in feet/toes
  - foreign bodies (IV, orthopedic pins)
  - systemic symptoms (fever, chills, malaise)
  - pain, tenderness, edema, erythema with poorly defined margins, regional lymphadenopathy
- can lead to ascending lymphangitis (visible red streaking in skin proximal to area of cellulitis)

**Investigations**
- CBC, blood cultures
- culture and Gram stain a collection/aspirate from wound if open wound
- plain radiographs cannot distinguish cellulitis from necrotizing fasciitis or gas gangrene but may help distinguish osteomyelitis

**Treatment**
- antibiotics: first line – cephalaxin 500 mg PO q6h or cloxacillin 500 mg PO q6h x 7 d; if complicated (e.g. lymphangitis, DM, severe infection, oral antibiotic therapy failure) consider IV cefazolin 1-2 g q8h or V cloxacillin, IV penicillin
- outline area of erythema to monitor success of treatment
- immobilize and splint (hands)
Necrotizing Fasciitis

Definition
- rapidly spreading, very painful infection of the fascia with necrosis of surrounding tissues
- some bacteria create gas that can be felt as crepitus and be seen on x-rays
- infection spreads rapidly along deep fascial plane and is limb and life threatening

Etiology
- Type I: polymicrobial (less aggressive)
- Type II: monomicrobial, usually β-hemolytic Streptococcus

Clinical Features
- pain out of proportion to clinical findings and beyond border of erythema
  - edema, tenderness, ± crepitus (subcutaneous gas from anaerobes)
  - overlying skin changes including blistering and ecchymoses
  - hyponatremia and hyperglycemia are common findings
  - patients may look deceptively well at first, but may rapidly become very sick/toxic
  - late findings
    - skin turns dusky blue and black (secondary to thrombosis and necrosis)
    - induration, formation of bullae
    - cutaneous gangrene, subcutaneous emphysema

Investigations
- a clinical diagnosis
- CT scan only if suspect it is not necrotizing fasciitis (looking for abscess, gas collection, myonecrosis and possible source of infection)
- severely elevated CK: usually means myonecrosis (late sign)
- bedside incision and exploration when ruling out conditions, clinical presentation is not supportive or difficult exam
- during incisional biopsy, often see "dish water pus" (Group A infection) and a hemostat easily passed along fascial plane (fascial biopsy to rule out in equivocal situations)

Treatment
- vigorous resuscitation (ABCs)
- urgent surgical debridement: remove all necrotic tissue, copious irrigation
- IV antibiotics: as appropriate for clinical scenario; consider penicillin 4 million IU IV q4h and/or clindamycin 900 mg IV q6h until final cultures available (the combination can be synergistic if Group A strep)
- possible role for IVIg (especially in Group A strep, adjuvant treatment on a case by case basis)
- urgent consultation with infectious disease specialist is recommended

Ulcers

Lower Limb Ulcers

Traumatic Ulcers (Acute)
- failure of wound to heal, usually due to compromised blood supply and unstable scar, secondary to pressure or bacterial colonization/infection
- usually over bony prominence ± edema ± pigmentation changes ± pain
- treatment: debridement of ulcer and compromised tissue, left to heal via secondary intention with dressings, may need reconstruction with local or distant flap in select cases, vascular status of limb must be assessed clinically and via vascular studies (i.e. ABI, duplex doppler)

Non-Traumatic Ulcers (Chronic)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% of vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause</td>
<td>Valvular incompetence</td>
<td>2nd to small and/or large vessel disease (be aware of risk factors)</td>
<td>Peripheral neuropathy: decreased sensation</td>
</tr>
<tr>
<td></td>
<td>Venous HTN</td>
<td></td>
<td>Atherosclerosis: microvascular disease</td>
</tr>
<tr>
<td>History</td>
<td>Dependent edema, trauma</td>
<td>Arteriosclerosis, claudication</td>
<td>DM</td>
</tr>
<tr>
<td></td>
<td>Rapid onset ± thrombophlebitis, varicosities</td>
<td>Usually &gt;45 yr Slow progression</td>
<td>Peripheral neuropathy</td>
</tr>
<tr>
<td></td>
<td>&quot;Gaiter&quot; locations</td>
<td></td>
<td>Trauma/pressure</td>
</tr>
<tr>
<td>Common Distribution</td>
<td>Medial malleolus</td>
<td>Distal locations (e.g. lower limb, feet)</td>
<td>Pressure point distribution (more likely feet)</td>
</tr>
</tbody>
</table>
Table 14. Venous vs. Arterial vs. Diabetic Ulcers (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Venous (70% of vascular ulcers)</th>
<th>Arterial</th>
<th>Diabetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appearance</td>
<td>Yellow exudates</td>
<td>Pale/white, necrotic base ± dry eschar covering</td>
<td>Necrotic base</td>
</tr>
<tr>
<td></td>
<td>Granulation tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Varicose veins</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brown discoloration of surrounding skin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound Margins</td>
<td>Irregular</td>
<td>Even (“punched out”)</td>
<td>Irregular or “punched out” or deep</td>
</tr>
<tr>
<td>Depth</td>
<td>Superficial</td>
<td>Deep</td>
<td>Superficial/deep</td>
</tr>
<tr>
<td>Surrounding Skin</td>
<td>Venous stasis discoloration (brown)</td>
<td>Thin shiny dry skin, hairless, cool</td>
<td>Thin dry skin ± hyperkeratotic border</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Hypersensitive/ischemic</td>
</tr>
<tr>
<td>Pulses</td>
<td>Normal distal pulses</td>
<td>Decreased or no distal pulses</td>
<td>Decreased pulses likely</td>
</tr>
<tr>
<td>Vascular Exam</td>
<td>ABI &gt;0.9 Doppler; abnormal venous system</td>
<td>ABI &lt;0.9 Pallor on elevation, rubor on dependency Delayed venous filling</td>
<td>ABI is inaccurately high (due to PVD) Usually associated with arterial disease</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>Moderately painful</td>
<td>Extremely painful Decreased with dependency, increased with leg elevation and exercise (claudication) Rest pain</td>
<td>Painless No claudication or rest pain Associated paresthesia, anesthesia</td>
</tr>
<tr>
<td>Treatment</td>
<td>Leg elevation, rest Compression at 30 mmHg (stockings or elastic bandages) Moist wound dressings ± topical, systemic antibiotics if infected ± skin grafts</td>
<td>Rest, no elevation, no compression Moist wound dressing ± topical and/or systemic antibiotics if infected Modify risk factors (smoking, diet, exercise, etc.) Vascular surgical consultation (angioplasty or bypass) Treat underlying conditions (DM, proximal arterial occlusion, etc.)</td>
<td>Control DM Careful wound care Foot care Orthotics Early intervention for infections (topical and/or systemic antibiotics if infected) Vascular surgical consultation</td>
</tr>
</tbody>
</table>

Pressure Ulcers

Common Sites
- over bony prominences; 95% on lower body

Stages of Development
1. hyperemia: disappears 1 h after pressure removed
2. ischemia: follows 2-6 h of pressure
3. necrosis: follows >6 h of pressure
4. ulcer: necrotic area breaks down – N.B. skin is like tip of an iceberg

Classification (National Pressure Ulcer Advisory Panel 2014)
- Stage I: nonblanchable erythema present >1 h after pressure relief, skin intact
- Stage II: partial-thickness skin loss
- Stage III: full-thickness skin loss into subcutaneous tissue
- Stage IV: full-thickness skin loss into muscle, bone, tendon, or joint
  - if an eschar is present, must fully debride before staging possible

Prevention
- good nursing care (clean dry skin, frequent repositioning), special beds or pressure relief surface, proper nutrition, activity, early identification of individuals at risk (e.g. immobility, incontinence, paraplegia, immunocompromised, DM etc.)

Treatment
- depends on individual patient and condition
- treat underlying medical issues including nutrition
- continue with preventative measures (pressure relief and assess for pressure points e.g. wheelchairs)
- wound debridement, moisture retentive or antimicrobial dressing, regular reassessment
- topical antimicrobials at treating physician’s discretion, systemic antibiotics for infections
- assess for possible reconstruction

Complications
- cellulitis, osteomyelitis, sepsis, gangrene
Burns

Burn Injuries

Causal Conditions
- thermal (flame contact, scald)
- chemical
- radiation (UV, medical/therapeutic)
- electrical

Most Common Etiology
- children: scald burns
- adults: flame burns

Table 15. Skin Function and Burn Injury

<table>
<thead>
<tr>
<th>Skin Function</th>
<th>Consequence of Burn Injury</th>
<th>Intervention Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thermoregulation</td>
<td>Prone to lose body heat</td>
<td>Must keep patient covered and warm</td>
</tr>
<tr>
<td>Control of fluid loss</td>
<td>Loss of large amounts of water and protein from the skin and other body tissues</td>
<td>Adequate fluid resuscitation is imperative</td>
</tr>
<tr>
<td>Mechanical barrier to bacterial invasion and immunological organ</td>
<td>High risk of infection</td>
<td>Antimicrobial dressings (systemic if signs of specific infection present) Tetanus prophylaxis if necessary</td>
</tr>
</tbody>
</table>

Pathophysiology of Burn Wounds

- amount of tissue destruction is based on temperature, time of exposure, and specific heat of the causative agent
- zone of hyperemia: vasodilation from inflammation; entirely viable, cells recover within 7 d; contributes to systemic consequences seen with major burns
- zone of stasis (edema): decreased perfusion; microvascular sludging and thrombosis of vessels results in progressive tissue necrosis → cellular death in 24-48 h without proper treatment
  - factors favouring cell survival: moist, aseptic environment, rich blood supply
  - zone where appropriate early intervention has most profound effect in minimizing injury
- zone of coagulation (ischemia): no blood flow to tissue → irreversible cell damage → cellular death/necrosis

Diagnosis and Prognosis

- burn size
  - % of TBSA burned: rule of 9s for 2° and 3° burns only (children <10 yr old use Lund-Browder chart)
  - for patchy burns, surface area covered by patient's palm (fingers closed) represents approximately 1% of TBSA
- age: more complications if <3 or >60 yr old
- depth: difficult to assess initially – history of etiologic agent and time of exposure helpful (see Table 16)
- location: face and neck, hands, feet, perineum are critical areas requiring special care of a burn unit (see Indications for Transfer to Burn Centre, PL18)
- inhalation injury: can severely compromise respiratory system
- associated injuries (e.g. fractures)
- comorbid factors (e.g. concurrent disability, alcoholism, seizure disorders, chronic renal failure) can exacerbate extent of injury

Prognosis best determined by
- burn size (TBSA)
- age of patient
- presence/absence of inhalational injury
Table 16. Burn Depth (1st, 2nd, 3rd degree)

<table>
<thead>
<tr>
<th>Nomenclature</th>
<th>Traditional Nomenclature</th>
<th>Depth</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema/Superficial</td>
<td>First degree</td>
<td>Epidermis</td>
<td>Painful, sensation intact, erythema, blanchable</td>
</tr>
<tr>
<td>Superficial-Partial Thickness</td>
<td>Second degree</td>
<td>Into superficial demis</td>
<td>Painful, sensation intact, erythema, blisters with clear fluid, blanchable, hair follicles present</td>
</tr>
<tr>
<td>Deep-Partial Thickness</td>
<td>Second degree</td>
<td>Into deep (reticular) demis</td>
<td>Insensate, difficult to distinguish from full thickness, does not blanch, some hair follicles still attached, softer than full thickness burn</td>
</tr>
<tr>
<td>Full Thickness</td>
<td>Third degree</td>
<td>Through epidermis and dermis injury to underlying tissue structures (e.g. muscle, bone)</td>
<td>Insensate (nerve endings destroyed), hard leathery eschar that is black, grey, white, or cherry red in colour, hairs do not stay attached, may see thrombosed veins</td>
</tr>
</tbody>
</table>
Indications for Transfer to Burn Centre

American Burn Association Criteria
- patients with partial or full-thickness burns that involve the hands, feet, genitalia, face, eyes, ears, and/or major joints or perineum
- partial thickness burns ≥20% TBSA in patients aged 10-50 yr old
- partial thickness burns ≥10% TBSA in children aged ≤10 or adults aged ≥50 yr old
- full thickness burns ≥5% TBSA in patients of all ages
- electrical burns, including lightening (internal injury underestimated by TBSA)
- chemical burns
- inhalation injury (high risk of mortality and may lead to respiratory distress)
- burn injuries in patients with medical comorbidities, could complicate management and recovery
- any patient with simultaneous trauma plus burns should be stabilized for trauma first, then triaged appropriately to burn centre
- any patients with burn injury and who will require special emotional, social, and rehabilitation intervention
- children with burns in a hospital not equipped with pediatric care specialists

Acute Care of Burn Patients
- adhere to ATLS protocol
- resuscitation using Parkland formula to restore plasma volume and cardiac output, Parkland formula is a starting estimate and patients may require more volume. Other formulas exist but the Parkland formula is predominately used in North America
  - 4 cc RL/kg/% TBSA over first 24 h (1/2 within first 8 h of sustaining burn, 1/2 in next 16 h)
- extra fluid administration required if
  - burn >80% TBSA
  - 4° burns
  - associated traumatic injury
  - electrical burn
  - inhalation injury
  - delayed start of resuscitation
  - pediatric burns
- monitor resuscitation
  - urine output is best measure: maintain at >0.5 cc/kg/h (adults) and 1.0 cc/kg/h (children <12 yr)
  - maintain a clear sensorium, HR <120/min, MAP >70 mmHg
- burn specific care
  - relieve respiratory distress: intubation and/or escharotomy
  - Escharotomy in circumferential extremity burn
  - prevent and/or treat burn shock: 2 large bore IVs for fluid resuscitation
  - insert Foley cather to monitor urine output
  - identify and treat immediate life-threatening conditions (e.g. inhalation injury, CO poisoning)
  - determine TBSA affected first, since depth is difficult to determine initially (easier to determine after 24 h)
- tetanus prophylaxis if needed
  - all patients with burns >10% TBSA, or deeper than superficial partial thickness, need 0.5 cc tetanus toxoid
  - also give 250 U of tetanus Ig if prior immunization is absent/unclear, or the last booster >10 yr ago
- baseline laboratory studies (Hb, U/A, BUN, CXR, electrolytes, ECG, cross-match if traumatic injury, ABG, carboxyhemoglobin)
- cleanse, debride, and treat the burn injury (antimicrobial dressings)
- early excision and grafting important for outcome

Respiratory Problems
- 3 major causes
  - burn eschar encircling chest
    - distress may be apparent immediately
    - perform escharotomy to relieve constriction
  - CO poisoning
    - may present immediately or later
    - treat with 100% O2 by facemask (decreases half-life of carboxyhemoglobin from 210 to 59 min) until carboxyHb <10%

Inhalation Injuries 101
- Indicators of inhalation injury
  - Injury in a closed space
  - Facial burn
  - Singed nasal hair/eyebrows
  - Soot around nares/oral cavity
  - Hoarseness
  - Conjunctivitis
  - Tachypnea
  - Carbon particles in sputum
  - Elevated blood CO levels (i.e. brighter red)
- Suspected inhalation injury requires immediate intubation due to impending airway edema; failure to diagnose inhalation injury can result in airway swelling and obstruction, which, if untreated, can lead to death
- Neither CXR or ABG can be used to rule out inhalation injury
- Direct bronchoscopy now used for diagnosis
- Signs of CO poisoning (headache, confusion, coma, arrhythmias)
- smoke inhalation leading to pulmonary injury
  - chemical injury to alveolar basement membrane and pulmonary edema (insidious onset)
  - risk of pulmonary insufficiency (up to 48 h) and pulmonary edema (48-72 h)
  - watch for secondary bronchopneumonia (3-25 d) leading to progressive pulmonary insufficiency
  - intubate patient with any signs of inhalation injuries

## Burn Wound Healing

### Table 17. Burn Shock Resuscitation (Parkland Formula)

| Hour 0-24 | 4 cc RL/kg/% TBSA with 1/2 of total in first 8 h from time of injury and 1/2 of total in next 16 h from time of injury |
| Hour 24-30 | 0.35-0.5 cc plasma/kg/TBSA |
| >Hour 30 | D5W at rate to maintain normal serum sodium |

*Do not forget to add maintenance fluid to resuscitation*

### Table 18. Burn Wound Healing

<table>
<thead>
<tr>
<th>Depth</th>
<th>Healing</th>
</tr>
</thead>
<tbody>
<tr>
<td>First degree (No scarring; complete healing)</td>
<td></td>
</tr>
<tr>
<td>Second degree (Superficial partial)</td>
<td>Spontaneously re-epithelialize in 7 to 14 d from retained epidermal structures ± residual skin discoloration</td>
</tr>
<tr>
<td>Deep second degree (Deep partial)</td>
<td>Re-epithelialize in 14-35 d from retained epidermal structures Hypertrophic scarring frequent</td>
</tr>
<tr>
<td>Third degree (Full thickness)</td>
<td>Re-epithelialize from the wound edge</td>
</tr>
<tr>
<td>Fourth degree</td>
<td>Often results in amputations If not requiring amputation, needs flap for coverage after debridement (do not re-epithelialize – cannot graft)</td>
</tr>
</tbody>
</table>

## Treatment

- 3 stages
  1. assessment: depth determined
  2. management: specific to depth of burn and associated injuries
  3. rehabilitation

- first degree
  - treatment aimed at comfort
    - topical creams (pain control, keep skin moist) ± aloe
    - oral NSAIDs (pain control)

- superficial second degree
  - daily dressing changes with topical antimicrobials (such as polysporin); leave blisters intact unless circulation impaired or unless over joint inhibiting motion

- deep second degree and third degree
  - prevent infection and sepsis (significant cause of death in burn patients)
    - most common organisms: *S. aureus, P. aeruginosa* and *C. albicans*
      - day 1-3 (rare): Gram-positive
      - day 3-5: Gram-negative (*Proteus, Klebsiella*)
    - topical antimicrobials: treat colonized wounds (from skin flora, gut flora or caregiver)
  - remove dead tissue
    - surgically debride necrotic tissue, excise to viable (bleeding) tissue

### Table 19. Antimicrobial Dressings for Burns

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Pain with Application</th>
<th>Penetration</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silver nitrate (0.5% solution)</td>
<td>None</td>
<td>Minimal</td>
<td>May cause methemoglobinemia, stains (black), leaches sodium from wounds</td>
</tr>
<tr>
<td>Nanocrystalline silver-coated dressing (Acticoat®)</td>
<td>None or transient</td>
<td>Medium, does not penetrate eschar</td>
<td>May stain, producing a pseudoeschar or facial discoloration (argyria-like symptoms); raised liver enzymes</td>
</tr>
<tr>
<td>Silver sulfadiazine (cream) (Silvadene®)</td>
<td>Minimal</td>
<td>Medium, penetrates eschar poorly</td>
<td>Slowed healing, leukopenia, mild inhibition of epithelialization</td>
</tr>
<tr>
<td>Mafenide acetate (solution/cream) (Sulfamylon®)</td>
<td>Moderate</td>
<td>Well, penetrates eschar</td>
<td>Mild inhibition of epithelialization, may cause metabolic acidosis with wide application</td>
</tr>
</tbody>
</table>

## Risk Factors for Infection of Burn Wounds

### Patient Related
- Extent >30% TBSA
- Depth: full-thickness and deep partial-thickness
- Patient age (higher risk with very young and very old)
- Comorbidities
- Wound dryness
- Wound temperature
- Secondary impairment of blood flow to wound
- Acidosis

### Microbial Factors
- Density >10⁵ organisms per gram tissue
- Motility
- Virulence and metabolic products (endotoxin, exotoxin, permeability factors, other factors)
- Antimicrobial resistance
• early excision and grafting is the mainstay of treatment for deep/full thickness burns
• initial dressing should decrease bacterial proliferation
• prevention of wound contractures: pressure dressings, joint splints, early physiotherapy

Other Considerations in Burn Management

Vascular Permeability and Edema
Immunosuppression
Renal Failure (2^nd to ↓ Renal Blood Flow)
SEVERE BURN

Altered Hemodynamics (↓ CO, ↑ SVR)
Hypermetabolism
Progressive Pulmonary Insufficiency
Increased Gut Mucosal Permeability
(GI Bleed Risk)

Figure 21. Systemic effects of severe burns

• nutrition
  - hypermetabolism: TBSA >40% have BMR 2-2.5x predicted
  - consider nutritional supplementation e.g. calories, vitamin C, vitamin A, Ca^{2+}, Zn^{2+}, Fe^{2+}
• immunosuppression and sepsis
  - must keep bacterial count <10^5 bacteria/g of tissue (blood culture may not be positive)
  - signs of sepsis: sudden onset of hyper/hypothermia, unexpected CHF or pulmonary edema, development of ARDS, ileus >48 h post-burn, mental status changes, azotemia, thrombocytopenia, hypofibrinogenemia, hyper/hypoglycemia (especially if burn >40% TBSA)
• GI bleed may occur with burns >40% TBSA (usually subclinical)
  - treatment: tube feeding or NPO, antacids, H2 blockers (preventative)
  - renal failure secondary to under resuscitation, drugs, myoglobin, etc.
  - progressive pulmonary insufficiency
    - can occur after: smoke inhalation, pneumonia, cardiac decompensation, sepsis
• wound contracture and hypertrophic scarring (outcomes optimized with timely wound closure, splinting, pressure garments) and physiotherapy

Special Considerations

CHEMICAL BURNS
• major categories: acid burns, alkaline burns, phosphorous burns, chemical injection injuries
• common agents: cement, hydrofluoric acid, phenol, tar
• mechanism of injury: chemical solutions coagulate tissue protein leading to necrosis
  - acids → coagulation necrosis
  - alkalines → saponification followed by liquefactive necrosis
• severity related to: type of chemical (alkali worse than acid), temperature, volume, concentration, contact time, site affected, mechanism of chemical action, degree of tissue penetration
• burns are deeper than they initially appear and may progress with time

Treatment (General)
• ABCs, monitoring
• remove contaminated clothing and brush off any dry powders before irrigation
• irrigation with water for 1-2 h under low pressure (contraindicated in heavy metal burns, such as sodium, potassium, magnesium, and lithium; in these cases soak in mineral oil instead)
• inspect eyes, if affected: wash with saline and refer to ophthalmology
• inspect nails, hair and webspaces
• correct metabolic abnormalities and tetanus prophylaxis if necessary
• local wound care 12 h after initial dilution (debridement)
• wound closure same as for thermal burn
• beware of underestimated fluid resuscitation, renal, liver, and pulmonary damage

Special Burns and Treatments

<table>
<thead>
<tr>
<th>Burn Type</th>
<th>Treatment Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acid Burn</td>
<td>Water irrigation, followed by dilute solution of sodium bicarbonate</td>
</tr>
<tr>
<td>Hydrofluoric Acid</td>
<td>Water irrigation; clip fingernails to avoid acid trapping; topical calcium gel ± subcutaneous injection of calcium gluconate ± 10% calcium gluconate IV depending on amount of exposure and pain</td>
</tr>
<tr>
<td>Sulfuric Acid</td>
<td>Treat with soap/lime prior to irrigation, as direct water exposure produces extreme heat</td>
</tr>
<tr>
<td>Tar</td>
<td>Remove with repeated application of petroleum-based antibiotic ointments (e.g. Polysporin®)</td>
</tr>
</tbody>
</table>
ELECTRICAL BURNS
- depth of burn depends on voltage and resistance of the tissue (injury more severe in tissues with high resistance)
- often presents as small punctate burns on skin with extensive deep tissue damage which requires debridement
- electrical burns require ongoing monitoring as latent injuries can occur
- watch for system specific damages and abnormalities
  - abdominal: intraperitoneal damage
  - bone: fractures and dislocations especially of the spine and shoulder
  - cardiopulmonary: anoxia, ventricular fibrillation, arrhythmias
  - muscle: myoglobinuria indicates significant muscle damage → compartment syndrome
  - neurological: seizures and spinal cord damage
  - ophthalmology: cataract formation (late complication)
  - renal: ATN resulting from toxic levels of myoglobin and hemoglobin
  - vascular: vessel thrombosis → tissue necrosis (increased Cr, K+ and acidity), decrease in RBC (beware of hemorrhages/delayed vessel rupture)
- Treatment
  - ABCs, primary and secondary survey, treat associated injuries
  - beware of cardiac arrhythmias (continue cardiac monitoring)
  - monitor: hemochromogenuria, compartment syndrome, urine output
  - wound management: topical agent with good penetrating ability (silver sulfadiazine or mafenide acetate)
  - debride non-viable tissue early and repeat prn (every 48 h) to prevent sepsis
  - amputations frequently required

FROSTBITE
- see Emergency Medicine, ER46

Hand

Traumatic Hand

Table 20. Key Features of the History and Physical Exam of the Injured Hand in the Emergency Department

<table>
<thead>
<tr>
<th>HISTORY</th>
<th>PHYSICAL EXAM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key Questions</td>
<td>Observation</td>
</tr>
<tr>
<td></td>
<td>Position of finger</td>
</tr>
<tr>
<td>Age</td>
<td>Abnormal cadence (fingers normally slightly flexed),</td>
</tr>
<tr>
<td>Hand dominance</td>
<td>scissoring</td>
</tr>
<tr>
<td>Occupation</td>
<td>Deformity</td>
</tr>
<tr>
<td>Time and place of accident</td>
<td>Bony protrusions or specific deformities (e.g. mallet,</td>
</tr>
<tr>
<td>Mechanism of injury</td>
<td>boutonniere, and swan neck deformity)</td>
</tr>
<tr>
<td>Tetanus status</td>
<td>Bruising or swelling</td>
</tr>
<tr>
<td></td>
<td>May indicate underlying skeletal injury</td>
</tr>
<tr>
<td></td>
<td>Sweating pattern (usually felt more so than from observation)</td>
</tr>
<tr>
<td></td>
<td>May indicate denervation</td>
</tr>
<tr>
<td></td>
<td>Anatomical structures beneath</td>
</tr>
<tr>
<td></td>
<td>If open laceration, need to explore within wound (under sterile conditions)</td>
</tr>
<tr>
<td>Structure</td>
<td>Examination</td>
</tr>
<tr>
<td>Radial and ulnar arteries</td>
<td>Allen’s Test</td>
</tr>
<tr>
<td>Digital arteries</td>
<td>Vascular Status</td>
</tr>
<tr>
<td>Temperature and skin turgor</td>
<td>Hard to palpate but you can assess capillary refill (&lt;2-3 s)</td>
</tr>
<tr>
<td></td>
<td>For each test, need to compare both sides</td>
</tr>
<tr>
<td>Sensory (see Figure 3)</td>
<td>Sensory (see Figure 3)</td>
</tr>
<tr>
<td>Median nerve</td>
<td>Median nerve</td>
</tr>
<tr>
<td>Ulnar nerve</td>
<td>Dorsal radial tip of index finger</td>
</tr>
<tr>
<td>Radial nerve</td>
<td>Ulnar nerve</td>
</tr>
<tr>
<td>Digital nerves</td>
<td>Dorsal web space of the thumb</td>
</tr>
<tr>
<td></td>
<td>2 point discrimination on both the radial and ulnar side of the DIPJ creases (static or moving 2 point discrimination)</td>
</tr>
</tbody>
</table>

Compartment Syndrome
Watch out for these signs with a closed or open injury: tense, painful extremity (worse on passive stretch), paresthesia/paralysis, pallor, distal pulselessness (often late in process), and contracture (irreversible ischemia)
Intracompartmental pressures can be measured (normal pressure = up to 12 mmHg), but a clinical diagnosis is an indication for an emergent fasciotomy; if untreated, end result is ischemic contracture of the extremity (Volkmann’s contracture)

Figure 22. Testing profundus (FDP) – inserts at distal phalanx
Figure 23. Testing superficialis (FDS) – inserts at middle phalanx
Table 20. Key Features of the History and Physical Exam of the Injured Hand in the Emergency Department (continued)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Examination</th>
</tr>
</thead>
</table>
| **Motor Function** | Flex DIP of index finger to test the anterior interosseous (AIN) branch of the median nerve  
Touch the tip of the index finger to the thumb trying to break through (“OK sign”)  
Thumb to ceiling with palm up |
| Median nerve | Ulnar nerve  
Extrinsic muscles: flex DIP of little finger  
Intrinsic muscles: abduct index finger ("Peace sign") or patient able to hold piece of paper between adducted fingers and resist pulling |
| Radial nerve | Extrinsic muscles: extend thumb ("thumb’s up") and wrist |
| **Range of Motion** | Assess active and passive range of motion of wrist  
extension/extension/ulnar/radial deviation, finger abduction/adduction/flexion/extension, thumb flexion/extension/adduction/adduction/circumflexion |
| Tendons, bones, joints, nerves | FDP  
Stabilize PIP in extension, ask patient to flex fingers (at DIP) |
| FDS | Stabilize non-exam fingers in extension (neutralizes FDP) and ask patient to flex examination finger |
| **Palpation** | Bones  
Focal tenderness or abnormal alignment |
| Joints | Instability may indicate ligamentous injury or dislocation |

**General Management**

**Nerves**
- test the nerve function BEFORE putting in local anesthesia
- direct repair for a clean injury within 14 d and without concurrent major injuries → otherwise secondary repair
- epineural repair of all digital nerves with minimal tension
- post-operative: dress wound, elevate hand and immobilize
- Tinel’s sign (cutaneous percussion over the repaired nerve) produces paresthesias and defines level of nerve regeneration
  - Wallerian degeneration occurs in the first 2 wk, which is why there is no Tinel’s sign till after this time period
  - a peripheral nerve regenerates at 1 mm/d
  - paresthesias felt at a area of percussion because re-growth of myelin (Schwann cells) is slower than axonal re-growth → percussion on exposed free-end of axon generates paresthesia

**Vessels**
- often associated with nerve injury (anatomical proximity)
- control bleeding with direct pressure and hand elevation
- if digit devascularized, optimal repair within 6 h
- close skin then dress, immobilize, and splint hand with fingertips visible
- monitor colour, capillary refill, skin turgor, fingertip temperature post-revascularization

**Tendons**
- most tendon lacerations require primary repair
- many extensors are repaired in the emergency room, flexors are repaired in the operating room within 2 wk
- avoid excessive immobilization after repair (specific protocols for flexors, 2-3 wk for extensors) to minimize stiffness and facilitate rehabilitation

**Bones**
- see Fractures and Dislocations, PL25

**Nailbed**
- remove nail to examine underlying nailbed under digital block anesthesia
- irrigate wound and nail thoroughly
- suture repair of nailbed with chromic suture
- replace cleaned nail, which acts as splint for any underlying distal phalangeal fracture and prevents adhesion formation between nail fold and nailbed

---

**Approach to Hand Lacerations**
- **TIN AX**
  - Tetanus prophylaxis
  - Irrigate with NS (copious irrigation and debridement in a timely manner)
  - NPO (NPO only if you are considering replanting, otherwise most operations are done as elective procedures)
  - Antibiotic prophylaxis (controversial – most require no ABx, mainly needed for animal bites)
  - X-rays

**Allen’s Test**: You need to exsanguinate the hand by having the patient open and close the hand. Then, while patient’s hand is firmly closed, occlude both radial and ulnar arteries. Once fist is open, release either artery and assess collateral flow

**Hand Exam**
- Never blindly clamp a bleeding vessel as nerves are often found in close association with vessels
- Never explore any volar hand wound in the ER
- Arterial bleeding from a volar digital laceration may indicate nerve laceration (nerves in digits are superficial to arteries)

**High pressure injection injury** is deceptively benign-looking (small pinpoint hole on finger pad) often with few clinical signs. Intense pain and tenderness, along the course the foreign material travelled, is present a few hours after the injury. Definitive treatment is exposure and removal of foreign material.
Hand Infections

Principles
- trauma is most common cause
- 5 cardinal signs: rubor (red), calor (hot), tumour (swollen), dolor (painful) and functio laesa (loss of function)
- 90% caused by Gram-positive organisms
- most common organisms (in order) – S. aureus, S. viridans, Group A Streptococcus, S. epidermidis, and Bacteroides melaninogenicus (MRSA is becoming more common)

TYPES OF INFECTIONS

Deep Palmar Space Infections
- uncommon, there are 9 spaces in the hand, the most commonly involved are thenar or mid-palm space (treated in the OR)

Felon
- definition: subcutaneous abscess in the fingertip that commonly occurs following a puncture wound into the pad of digit; may be associated with osteomyelitis (skin to compartment syndrome and can lead to skin necrosis)
- treatment: elevation, warm soaks, cloxacillin 500 mg PO q6h (if in early stage); if obvious abscess or pressure on the overlying skin or failure to resolve with conservative measures, then needs I&D; take cultures/gram stain and PO cloxacillin

Flexor Tendon Sheath Infection
- Staphylococcus > Streptococcus > Gram-negative rods
- definition: acute tenosynovitis commonly caused by a penetrating injury and can lead to tendon necrosis and rupture if not treated; it is often suppurative; however, early on there can be very little pus
- clinical features: Kanavel’s 4 cardinal signs
  1. point tenderness along flexor tendon sheath (earliest and the most sensitive and specific)
  2. severe pain on passive extension of DIP (second most important)
  3. fusiform swelling of entire digit
  4. flexed posture (increased comfort)
- treatment
  - OR incision and drainage, irrigation, IV antibiotics, and resting hand splint until infection resolves

Herpetic Whitlow
- HSV-1, HSV-2
- definition: painful vesicle(s) around fingertip
  - often found in medical/dental personnel and children
- clinical features: can be associated with fever, malaise and lymphadenopathy
- patient is infectious until lesion has completely healed
- treatment: routine culture and viral prep protection (cover), consider oral acyclovir; do not break blisters, as this can spread infection

Paronychia
- acute = Staphylococcus; chronic = Candida
- definition: infection (granulation tissue) of soft tissue around fingernail (beneath eponychial fold)
- etiology
  - acute paronychia: a “hangnail”, artificial nails, and nail biting
  - chronic paronychia: prolonged exposure to moisture
- treatment
  - acute paronychia: warm compresses and cephalaxin 500 mg PO q6h if caught early and drainage if abscess present – can usually drain with a #11 blade directed into the abscess from underneath the paronychial fold
  - chronic paronychia: anti-fungals with possible debridement and marsupialization, removal of nail plate

Amputations

Hand or Finger
- emergency management: injured patient and amputated part require attention
  - patient: x-rays (stump and amputated part), NPO, clean wound and irrigate with NS, dress stump with nonadherent, cover with dry sterile dressing, tetanus and antibiotic prophylaxis (cephalosporin/erythromycin)
  - amputated part: x-rays, gently irrigate with RL, wrap amputated part in a NS/RL soaked sterile gauze and place inside waterproof plastic bag, place in a container, then place container on ice
• indications for replantation
  - age: children often better results than adults
  - level of injury: proximal, thumb and multiple digit amputations are higher priority
  - nature of injury: clean cut injuries have higher successful replantation rate; avulsion and crush injuries are relative contraindications to replant
  - if replant contraindicated manage stump with revision amputation
    - would only allow a fingertip injury to heal by secondary intention

## Tendons

### Common Extensor Tendon Deformities

<table>
<thead>
<tr>
<th>Injury</th>
<th>Definition</th>
<th>Zone</th>
<th>Etiology/Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mallet Finger</td>
<td>DIP flexed with loss of active extension</td>
<td>1</td>
<td>There are bony and non-bony mallets. Bony: Fracture of distal phalanx distal to tendon insertion. Non-bony: Forced flexion of the extended DIP leading to extensor tendon rupture at DIP (e.g. sudden blow to tip of the finger).</td>
<td>Splint DIP in extension for 6 wk followed by 2 wk of night splinting; if inadequate improvement after 6 wk, check splinting routine and recommend 4 more wk of continuous splinting. If there is a bony component that is displaced the patient may require ORIF.</td>
</tr>
<tr>
<td>Boutonniere Deformity</td>
<td>PIP flexed, DIP hyperextended</td>
<td>3</td>
<td>Injury or disease affecting the extensor tendon insertion into the dorsal base of the middle phalanx. Associated with RA or trauma (laceration, volar dislocation, acute forceful flexion of PIP)</td>
<td>Splint PIP in extension and allow active DIP motion.</td>
</tr>
<tr>
<td>Swan Neck Deformity</td>
<td>PIP hyperextended, DIP flexed</td>
<td>3</td>
<td>Trauma (PIP volar plate injury). Associated with RA and old, untreated mallet deformity.</td>
<td>Splint to prevent PIP hyperextension or DIP flexion. Consider arthrodesis/arthroplasty.</td>
</tr>
</tbody>
</table>

De Quervain’s Tenosynovitis (zone 7; most common cause of radial wrist pain)
- definition: inflammation in 1st extensor compartment (APL and EPB)
- clinical features
  - +ve Finkelstein’s test (pain over the radial styloid induced by making fist, with thumb in palm, and ulnar deviation of wrist)
  - pain localized to the 1st extensor compartment
  - tenderness and crepitation over radial styloid may be present
  - differentiate from CMC joint arthritis (CMC joint arthritis will have a positive grind test, whereby crepitus and pain are elicited by axial pressure to the thumb)
- treatment
  - mild: NSAIDs, splinting and steroid injection into the tendon sheath (successful in over 60% of cases)
  - severe: surgical release of stenotic tendon sheaths (APL and EPB); remember there may be 2 or more sheaths

Ganglion Cyst
- definition
  - fluid-filled synovial lining that protrudes between carpal bones or from a tendon sheath; most commonly carpal in origin
  - most common soft tissue tumour of hand and wrist (60% of masses)
- clinical features
  - most common around scapholunate ligament junction
  - 3 times more common in women than in men
  - more common in younger individuals
  - can be large or small – may drain internally so size may wax and wane
  - often non-tender although tenderness increased when cyst smaller (from increased pressure within smaller cyst sac)
• treatment
  ▪ conservative treatment: do nothing
  ▪ aspiration (recurrence rate 65%)
  ▪ consider operative excision of cyst and stalk (recurrence is possible)
  ▪ steroids if painful (done in combination with aspiration)

Common Flexor Tendon Deformities
• flexor tendon zones (important for prognosis of tendon lacerations)
  ▪ “no-man’s land”
    ▪ between distal palmar crease and mid-middle phalanx
    ▪ zone where superficialis and profundus lie ensheathed together
  ▪ recovery of glide very difficult after injury

Stenosing Tenosynovitis (trigger finger/thumb)
• definition: inflammation of synovium causes size discrepancy between tendon and sheath/pulley (most commonly at A-1 pulley) = locking of thumb or finger in flexion/extension
• etiology: idiopathic or associated with RA, DM, hypothyroidism and gout
• clinical features
  ▪ thumb, ring and long fingers most commonly affected
  ▪ patient complains of catching, snapping or locking of affected finger
  ▪ tenderness to palpation/nodule at palmar aspect of MCP over A-1 pulley
  ▪ women are 4 times more likely than men to be affected
• conservative treatment
  ▪ NSAIDs
  ▪ steroid injection
  ▪ injections less likely to be successful in patients with DM or symptoms greater than 6 mo
  ▪ splint
• surgical treatment
  ▪ indicated if no relief of symptoms or minimal relief with steroids
  ▪ incise A-1 flexor tendon pulley to permit unrestricted, full active finger motion

Fractures and Dislocations

• for fracture principles, see Orthopedics, OR4

FRACTURES
• about 90% of hand fractures are stable in flexion (splint to prevent extension)
• position of function (like a hand holding a pop can)
  ▪ wrist extension 15°
  ▪ MCP flexion 45°
  ▪ IP flexion (slight)
  ▪ thumb abduction/rotation
  ▪ done if you wanted to immobilize a fracture but are were unsure if there were other injuries
  ▪ contraindications: post repair of flexor tendons, median/ulnar nerve injury
  ▪ stiffness secondary to immobilization is the most important complication; T x = early motion

Distal Phalanx Fractures
• most commonly fractured bone in the hand
• usual mechanism is crush injury and thus accompanied by soft tissue injury
• subungual hematoma is common and must be decompressed if painful by removing the nail
• treatment consists of 3 wk of digital splinting (with IP joint movement preserved)

Proximal and Middle Phalanx Fractures
• check for: rotation, scissoring (overlap of fingers on making a fist), shortening of digit
  ▪ undisplaced or minimally displaced: closed reduction (if extra-articular) buddy tape to neighbouring stable digit, elevate hand, motion in guarded fashion early, splinted for 2-3 wk
  ▪ displaced, non-reducible, not stable with closed reduction, or rotational or scissoring deformity: percutaneous pins (K-wires) or ORIF, and splint

Metacarpal Fractures
• generally accept varying degrees of deviation before reduction required: up to 10° (D2), 20° (D3), 30° (D4), or 40° (D5)
• Boxer’s fracture (extra-articular): acute angulation of neck of metacarpal of little finger into palm
  ▪ mechanism: blow on the distal-dorsal aspect of closed fist
  ▪ loss of prominence of metacarpal head, volar displacement of head
  ▪ check for scissoring of fingers on making a fist
  ▪ up to 30-40° angulation may be acceptable
  ▪ closed reduction should be considered to decrease the angle
  ▪ if stable ulnar gutter splint for 2-3 wk

Grading classification for Stenosing Tenosynovitis
• Grade I (Pre-triggering)- Pain/ tenderness over the A1 pulley with a hx of catching although not catching on exam
• Grade II (Active)- Demonstrable catching, but the patient can extend the finger
• Grade III (Passive)- Grade IIIa: catching requiring passive extension. Grade IIIb is the inability to actively flex
• Grade IV (Contracture)- Catching with a fixed flexion contracture of the proximal interphalangeal joint
• **Bennett's fracture (intra-articular):** fracture/dislocation of the base of the thumb metacarpal
  - unstable fracture
  - abductor pollicis longus pulls MC shaft proximally and radially causing adduction of thumb
  - treat with percutaneous pinning, thumb spica x 6 wk
• **Rolando's fracture (intra-articular):** T- or Y-shaped fracture of the base of the thumb metacarpal
  - treated like a Bennett's fracture

### DISLOCATIONS
- must be reduced as soon as possible
- dislocation vs. subluxation
  - dislocation: severe injury where articular surfaces of a joint are no longer in contact with one another
  - subluxation: articular surfaces of a joint are partially out of place, but then go back into place (partial dislocation, often unstable)

### PIP and DIP Dislocations (PIP more common than DIP)
- usually dorsal dislocation (commonly from hyperextension)
- if closed dislocation: closed reduction and splinting (30° flexion for PIP and full extension for DIP) or buddy taping and early mobilization (prolonged immobilization causes stiffness)
- open injuries are treated with wound care, closed or open reduction, irrigation and debridement, and antibiotics

### MCP Dislocations (relatively rare)
- dorsal dislocations much more common than volar dislocations
- dorsal dislocation of proximal phalanx on metacarpal head; most commonly index finger (hyperextension)
- two types of dorsal dislocation
  - simple (reducible with manipulation): treat with 2-4 wk of splinting at 30° MCP flexion
  - complex (volar plate blocks reduction): treat with open reduction and A1 pulley release + extension-blocking splint at 30° flexion (2 wk) then 10° flexion (2 wk)

### Ulnar Collateral Ligament (UCL) Injury
- forced abduction of thumb (e.g. ski pole injury)
- **skier's thumb:** acute UCL injury
- **gamekeeper's thumb:** chronic UCL injury
- **evaluation:** radially deviate thumb MCP joint in full extension and at 30° flexion and compare with non-injured hand. UCL rupture is presumed if injured side deviates more than 30° in full extension or more than 15° in flexion
- **Stener's lesion:** the UCL has bony attachments to the adductor aponeurosis and the proximal ligament can displace while the distal attachment remains deep to the aponeurosis, forming a barrier that blocks healing and leads to chronic instability; requires surgery

### Dupuytren's Disease

#### Definition
- contraction of longitudinal palmar fascia, forming nodules (usually painless), fibrous cords and eventually flexion contractures at the MCP and interphalangeal joints
- flexor tendons not involved
- Dupuytren's diathesis: early age of onset, strong family history, and involvement of sites other than palmar aspect of hand

#### Epidemiology
- genetic disorder, unusual in patients from African and Asian countries, high incidence in northern Europeans, men > women, often presents in 5th-7th decade of life, associated with but not caused by alcohol use and DM

#### Clinical Features
- order of digit involvement (most common to least common): ring > little > long > thumb > index
- may also involve feet (Ledderhose's) and penis (Peyronie's – see Urology, U30)

#### Treatment
- stages
  1. palmar pit or nodule: no surgery
  2. palpable band/cord with no limitation of extension of either MCP or PIP: no surgery
  3. lack of extension at MCP or PIP: surgical fasciectomy indicated
  4. irreversible periarticular joint changes/scarring: surgical treatment possible but poorer prognosis compared to stage 3
Carpal Tunnel Syndrome

**Definition**
- median nerve compression at the level of the flexor retinaculum as opposed to pronator teres syndrome (compressive neuropathy at the level of the elbow)

**Etiology**
- median nerve entrapment at wrist
- primary cause is idiopathic
- secondary causes: space occupying lesions (tumours, hypertrophic synovial tissue, fracture callus, and osteophytes), metabolic and physiological (pregnancy, hypothyroidism, acromegaly, and RA), infections, neuropathies (associated with DM or alcoholism), and familial disorders
- job/hobby related repetitive trauma, especially forced wrist flexion

**Epidemiology**
- female:male = 4:1, most common entrapment neuropathy

**Clinical Features**
- sensory loss in median nerve distribution (see Figure 4)
- discriminative touch often lost first
- classically, patient awakened at night with numb/painful hand, relieved by shaking/dangling/ rubbing
- decreased light touch and 2-point discrimination, especially fingertips
- advanced cases: thenar wasting/weakness due to involvement of the motor branch of the nerve
- ± Tinel's sign (tingling sensation on percussion of nerve)
- ± Phalen's sign (wrist flexion induces symptoms)

**Investigations**
- clinical diagnosis
- NCV and EMG may confirm, but do not exclude, the diagnosis

**Treatment**
- avoid repetitive wrist and hand motion, wrist splints at night and when repetitive wrist motion required
- conservative: night time splinting to keep wrist in neutral position
- medical: NSAIDs, local corticosteroids injection, oral corticosteroids
- surgical decompression: transverse carpal ligament incision to decompress median nerve
- indications for surgery: numbness and tingling ± sensory loss, weakness ± muscle atrophy, unresponsive to conservative measures
- complications of surgery: injury to median motor branch, palmar cutaneous branch or superficial transverse vascular arch, local pain (pain at wrist flexion)

Rheumatoid Hand

- see Rheumatology: RH8

Brachial Plexus

**Etiology**
- common causes of brachial plexus injury: complication of childbirth and trauma
- other causes of injury: compression from tumours, ectopic ribs

**Common Palsies**

<table>
<thead>
<tr>
<th>Palsy</th>
<th>Location of Injury</th>
<th>Mechanism of Injury</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duchenne-Erb Palsy</td>
<td>Upper brachial plexus (C5-C6)</td>
<td>Head/shoulder distraction (e.g. motorcycle)</td>
<td>“Waiter’s tip deformity” (shoulder internal rotation, elbow extension, wrist flexion)</td>
</tr>
<tr>
<td>Klumpke’s Palsy</td>
<td>Lower brachial plexus (C7-T1)</td>
<td>Traction on abducted arm</td>
<td>“Claw hand” May include Homer’s syndrome</td>
</tr>
</tbody>
</table>

Development and Validation of Diagnostic Criteria for Carpal Tunnel Syndrome

**J Hand Surg 2006;31:919-924**

**Purpose:** To develop a clinical diagnostic criteria for carpal tunnel syndrome that modeled the clinical diagnostic practices of experts.

**Methods:** Out of 57 clinical findings associated with CTS, eight were ranked highly by a panel of expert clinicians. Using 256 case histories, a panel of experts decided whether a case did or did not have a diagnosis of CTS. This diagnosis represented the dependent variable for a logistic regression model, to which the eight clinical findings were applied. The regression model was then validated against the consensus of a second panel on the diagnosis of CTS for the case histories.

**Results/Conclusions:** The correlation between the probability of CTS predicted by the regression model and the panel of clinicians was 0.71. Clinical diagnostic criteria that contributed significantly to the model were:

1. Numbness and tingling in median nerve distribution
2. Nocturnal numbness
3. Weakness and/or atrophy of the thenar musculature
4. Tinel’s sign
5. Phalen’s test
6. Loss of 2-point discrimination

A Cochrane Review looked at non-surgical management of carpal tunnel and found that there is significant short-term benefit from oral steroids, splinting, ultrasound, yoga, and carpal bone mobilization.

Cochrane Database Systematic Review 2003: CD001279

Radiographic Evolution of the Rheumatoid Hand

**Earliest Sign:** erosion of the ulnar styloid

**Progression:** characterized by symmetrical joint space narrowing and erosions of the carpal bones, MCP and PIP (with DIP relatively spared)

**Late Stage:** Swan neck and Boutonniere deformities
Differential Diagnosis of Adult Acquired Brachial Plexus Palsies

- trauma (blunt, penetrating)
- thoracic outlet syndrome
  - neurogenic: associated with cervical rib; compression of C8/T1
  - vascular: pain or sensory symptoms without cervical rib; cessation of radial pulse with provocative maneuvers
- tumour
  - schwannoma: well-defined margins makes it easier for total resection
  - neurofibromas: associated with neurofibromatosis type I
  - other: e.g. Pancoast syndrome (apical lung tumour)
- neuropathy (compressive, post-irradiation, viral, diabetic, idiopathic)

Investigations

- EMG
- CT myelogram: controversial, although some people think that it is better than MRI for identification of nerve root avulsion and identification of pseudomeningocele. Important for pre-operative identification of patients likely to require neurotisation procedures (especially for patients with blunt trauma)
- timing for investigations and surgery is important. First studies are likely not done until 6 wk after a closed injury; however, any open injury will go to the OR for immediate exploration

Management

<table>
<thead>
<tr>
<th>Type</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Penetrating Trauma</td>
<td></td>
</tr>
<tr>
<td>Concussive/compressive</td>
<td>Usually improves (unless expanding mass, e.g. hematoma)</td>
</tr>
<tr>
<td>Traction/stretch</td>
<td>If no continued insult, follow for 3-4 mo for improvement</td>
</tr>
<tr>
<td>Obstetric palsy</td>
<td>Surgery if no significant improvement and/or residual paresis at 6 mo of age</td>
</tr>
<tr>
<td>Penetrating Trauma</td>
<td></td>
</tr>
<tr>
<td>Sharp or vascular injury</td>
<td>Explore immediately in OR</td>
</tr>
</tbody>
</table>

Craniofacial Injuries

- low velocity vs. high velocity injuries determine degree of damage
- fractures cause bruising, swelling and tenderness → loss of function
- frequency: nasal > zygomatic > mandibular > maxillary
- management: can wait 5-10 d for swelling to decrease before ORIF required

Approach to Facial Injuries

- ATLS protocol
- inspect, palpate, clinical assessment for injury to underlying structures (e.g. facial nerve)
- tetanus prophylaxis
- radiological evaluation
- wound irrigation with NS/RL and remove foreign materials
- conservative debridement of detached or nonviable tissue
- repair when patient’s general condition allows (soft tissue injury: <8 h preferable)
- suspect C-spine injury with any facial trauma. C-spine evaluation should be done before radiographs are ordered
- consider intracranial trauma; rule out skull fracture

Investigations

- CT
  - axial and coronal (specifically request 1.5 mm cuts): for fractures of upper and middle face
  - indicated for significant head trauma, complex facial fractures, orbital floor, panface fractures, pre-operative assessment
- panorex radiograph: shows entire upper and lower jaw; best for isolated mandible fracture but patient must be able to sit
Table 24. Imaging of the Craniofacial Skeleton

<table>
<thead>
<tr>
<th>Structure</th>
<th>Appropriate Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mandible</td>
<td>Panoramic (panorex)</td>
</tr>
<tr>
<td></td>
<td>CT</td>
</tr>
<tr>
<td>Zygomatic and orbital bones</td>
<td>CT scan</td>
</tr>
<tr>
<td>Nasal bones</td>
<td>No x-ray required – clinical</td>
</tr>
<tr>
<td>Maxilla</td>
<td>CT scan - axial and coronal</td>
</tr>
</tbody>
</table>

**Treatment Goals**

- consultation when indicated (dentistry, ophthalmology)
- re-establish normal occlusion if occlusion is an issue
- pursue normal eye function (extraocular eye movements and vision)
- restore stability of face and appearance

**Complications**

- complications are dependent on the surgery and injury. Not all complications apply to all situations
- diplopia/enophthalmos/blindness
- intracranial pathology such as CSF leak, bleeding and SIADH (secondary to trauma, not the surgery itself)
- sinusitis
- functional abnormalities (i.e. malocclusion)
- infection – extremely rare
- poor cosmesis; need for 2nd surgery

---

**Mandibular Fractures**

- always two points of injury since it is a ring structure (includes fractures and dislocations)
- commonly at sites of weakness (condylar neck, angle of mandible, region of 3rd molar or canine tooth)

**Etiology**

- anterior force: bilateral fractures
- lateral force: ipsilateral subcondylar and contralateral angle or body fracture
- note: classified as open if fracture into tooth bearing area (alveolus)

**Clinical Features**

- pain, swelling, difficulty opening mouth (“trismus”)
- malocclusion, asymmetry of dental arch
- damaged, loose, or lost teeth
- palpable “step” along mandible
- numbness in V3 distribution
- intra-oral lacerations or hematoma (sublingual)
- chin deviating toward side of a fractured condyle

**Classification**

Table 25. Mandibular Fracture Classifications by Anatomic Region

<table>
<thead>
<tr>
<th>Areas/Boundaries</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symphysis</td>
<td>Midline of the mandible; between the central incisors from the alveolar process through the inferior border of the mandible</td>
</tr>
<tr>
<td>Body</td>
<td>From the symphysis to the distal alveolar border of the third molar</td>
</tr>
<tr>
<td>Angle</td>
<td>Triangular region between the anterior border of the masseter and the posterosuperior insertion of the masseter distal to the third molar</td>
</tr>
<tr>
<td>Ramus*</td>
<td>Part of the mandible that extends posterosuperiorly into the condylar and coronoid processes</td>
</tr>
<tr>
<td>Condylar*</td>
<td>Area of condylar process of mandible</td>
</tr>
<tr>
<td>Subcondylar</td>
<td>Area below the condylar neck (i.e. sigmoid notch) of the mandible</td>
</tr>
<tr>
<td>Coronoid Process</td>
<td>Area of the coronoid process of mandible</td>
</tr>
</tbody>
</table>

*Most common mandibular fracture type
Treatment
• maxillary and mandibular arch bars wired together (intramaxillary fixation) or ORIF
• antibiotics to cover against *S. aureus* and anaerobes

Complications
• malocclusion, malunion
• tooth loss, and possible sensation loss
• TMJ ankylosis

Maxillary Fractures

<table>
<thead>
<tr>
<th>Table 26. Le Fort Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Le Fort I</td>
</tr>
<tr>
<td>Alternative Name</td>
</tr>
<tr>
<td>Type of Fracture</td>
</tr>
<tr>
<td>Structures Involved</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anatomical Result</td>
</tr>
</tbody>
</table>

Nasal Fractures

Etiology
• lateral force ➔ more common, good prognosis
• anterior force ➔ can produce more serious injuries
• most common facial fracture

Clinical Features
• epistaxis/hemorrhage, deviation/flattening of nose, swelling, periorbital ecchymosis, tenderness over nasal dorsum, crepitus, septal hematoma, respiratory obstruction, subconjunctival hemorrhage
• depression and splaying of nasal bones causing a saddle deformity
• important to clinically assess for naso-orbital ethmoid fractures

Treatment
• treated for airway or cosmetic issues
• closed reduction with Asch or Walsham forceps under anesthesia, pack nostrils with petroleum or non-adhesive gauze packing, nasal splint for 7 d
• best reduction immediately (<6 h) or when swelling subsides (5-7 d)
• rhinoplasty may be necessary later for residual deformity (30%)

Naso-Orbital Ethmoid Fractures

Etiology
• fractures of the nasal and ethmoid bones of the medial orbit
• problematic and may lead to change in facial appearance
• Markowitz-Manson classification:
  ▪ Type 1: Single, central fragment, medial canthal ligament intact
  ▪ Type 2: Comminuted central fragment, medial canthal ligament intact
  ▪ Type 3: Severe comminution of central fragment and disrupted medial canthal ligament

Clinical Presentation
• telecanthus defined as increased intercanthal distance secondary to medial canthal ligament disruption
• orbital rim step-off

Treatment
• surgical repair to restore intercanthal distance (reverse telecanthus), nasal projection and orbital anatomy

Always drain septal hematomas as this is a cause of septal necrosis with perforation (saddle nose deformity)
Zygomatic Fractures

- Classification
  1. Fracture restricted to zygomatic arch
  2. Depressed fracture of zygomatic complex (zygoma)
  3. Unstable fracture of zygomatic complex (tetrapod fracture) – separations occur at maxilla, frontal bone, temporal bone and orbital rim

Clinical Features
- Flattening of malar prominence (view from above)
- Pain over fractures on palpation
- Numbness in V2 distribution (infraorbital and superior dental nerves)
- Palpable step deformity in bony orbital rim (especially inferiorly)
- Often associated with fractures of the orbital floor
- Ipsilateral epistaxis; trismus

Treatment
- If undisplaced, stable and no symptoms, then soft diet; no treatment necessary
- Ophthalmologic evaluation if suspected globe injury
- Undisplaced zygomatic arch fractures can be elevated using Gillies approach: leverage on the anterior part of the zygomatic arch via a temporal incision; stabilization often unnecessary
- ORIF for displaced or unstable fractures of zygomatic complex

Orbital Floor Fractures

- See Ophthalmology, OP43

Definition
- Fracture of floor of orbit ± intact infraorbital rim
- May be associated with nasoethmoid fracture

Etiology
- Blunt force to eyeball → sudden increase in intra-orbital pressure (e.g. baseball or fist)

Clinical Features
- Check visual fields and acuity for injury to globe
- Periorbital edema and bruising, subconjunctival hemorrhage
- Ptosis, exophthalmos, exorbitism, or enophthalmos
- Orbital rim step-offs with possible infraorbital nerve anesthesia
- Vertical dystopia (abnormal displacement of the entire orbital cone in the vertical plane); diplopia looking up or down (entrapment of inferior rectus), limited EOM
- Orbital entrapment
  - Clinical diagnosis that is a surgical emergency
  - Diplopia with vertical gaze; limited EOM
  - Severe pain or nausea and vomiting with upward globe movement
  - Requires urgent ophthalmologic evaluation and surgical repair

Investigations
- CT (diagnostic): axial and coronal views
- Diagnostic manoeuvre for entrapment is forced duction test (pulling on inferior rectus muscle with forceps to ensure full ROM) under anesthesia in the OR

Treatment
- Surgical repair indicated if: Urgent repair for entrapment, floor defect >1 cm, any size defect with enophthalmos or persistent diplopia (>10 d)
- Reconstruction of orbital floor with bone graft or alloplastic material
- Ophthalmologic evaluation suggested

Complications
- Persistent diplopia
- Enophthalmos

Superior Orbital Fissure Syndrome
- Fracture of SOF causing ptosis, proptosis, anesthesia in V1 distribution, and painful ophthalmoplegia (paralysis of CN III, IV, VI)
- Uncommon complication seen in Le Fort II and III fractures (1/130)
- Recovery time reported as 4.8-23 wk following operative reduction of fractures

Orbital Apex Syndrome
- Fracture through optic canal with involvement of CN II at apex of orbit
- Symptoms are the same as SOF syndrome plus vision loss
- Treatment is urgent decompression of fracture in optic canal (posterior craniotomy for decompression) or steroids
Breast Surgery

Breast Reconstruction

• important consideration in breast cancer treatment
• two basic methods: implants (1-stage or 2-stage) or autologous tissue
• may also require breast balancing procedure and nipple areola reconstruction

Pre-Reconstruction Considerations

• radiation: treatment before and after mastectomy is a relative contraindication to alloplastic reconstruction
• recipient tissue: skin sparing mastectomy allows for the use of implants without tissue expanders
• donor tissue: limited availability of suitable donor tissue (lack of tissue, scar, previous surgery that interferes with blood supply) may prevent the use of autologous tissue reconstruction
• timing (immediate vs. delayed)
• contralateral breast: may not be possible to reconstruct a breast of the same size or shape as the contralateral breast. Breast reduction or mastopexy may be considered in opposite breast (see Table 28)
• other considerations: patient’s comorbidities, prognosis, body weight, characteristics of chest wall and patient’s attitude

Table 27. Options for Breast Reconstruction

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Definition</th>
<th>Surgical Details</th>
<th>Other Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alloplastic</td>
<td>Use of synthetic material (silicone or saline implants)</td>
<td>With expanders (2 stages): Use tissue expanders before replacement with implants to facilitate breast ptosis Without expanders (1 stage): In skin-sparing mastectomy, enough skin is available for immediate placement of implant. The limiting factor, however, is the muscle as the implant must fit under the pectoralis (may require acellular dermal matrix if implant size and muscle size is a mismatch)</td>
<td>Complications: capsular contraction (foreign body reaction to implants), rupture or leakage of implant, increased risk of infection, 35% revision rate over 5 yr</td>
</tr>
<tr>
<td>(Implant based)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autologous Tissue</td>
<td>Use of patient’s own tissue</td>
<td>Many flap options: DIEP, TRAM, latissimus dorsi, SIEA, SGAP, and IGAP</td>
<td>Offers natural consistency</td>
</tr>
<tr>
<td>Nipple Areola</td>
<td>Final stage of breast reconstruction</td>
<td>Local vs. distant flap/graft: 1. Local: fish tail, skate, top hate, double opposing etc.; these flaps allow simultaneous nipple and areola reconstruction 2. Distant: opposite nipple, earlobe, abdominal skin, costal cartilage, labia</td>
<td>Usually performed 3 mo post-reconstruction</td>
</tr>
</tbody>
</table>

Breast Tissue Expanders

• types: textured vs. smooth, both with integrated port
• placement: sub-pectoral, total submuscular (pectoral/serratus)
• size: depends on contralateral breast and desired size
  * generally over-expanded to facilitate ptosis
• timing of expansion: begins when wound fully healed (usually 2 wk post-operative), and tissue expanders are inflated weekly or bi-weekly until complete (up to 3 mo); expanders are exchanged for implants after another 3 mo for consolidation of expanded skin

Arterial blood supply to the breast

• internal thoracic*
• external thoracic*
• lateral thoracic
  * thoracoacromial
  * intercostals
  * thoracodorsal
• also provide arterial blood supply to nipple-areola complex

Figure 37. Augmentation mammoplasty: incision lines and implant placement

Patients may require a balancing procedure on contralateral side

Nipple innervation is T4
Breast Reduction

- reduction mammoplasty performed for relief of physical symptoms (e.g. shoulder groove, neck pain, back pain, shoulder pain, mastodynia)
- key steps of procedure include preoperative landmarks, design of pedicle, nipple preservation, tissue resection, breast reshaping, setting nipple at aesthetic landmark, and tension free closure
  - incisions: circular around the areola, vertical from areola incision to infra-mammary fold, along the natural infra-mammary fold (this incision is for a wise pattern reduction, although many other types exist)
  - removal of fat, breast tissue, and excess skin
  - need to move nipple and areola complex to higher position
- complications: infection, hemorrhage, decreased nipple sensation, inability to breast feed, breast/nipple asymmetry, nipple loss (partial or complete), skin loss/necrosis, fat necrosis

Aesthetic Surgery

Aesthetic Procedures

Table 28. Aesthetic Procedures

<table>
<thead>
<tr>
<th>Location</th>
<th>Procedure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head/Neck</td>
<td>Hair transplants</td>
<td>Aesthetic improvement of hair growth patterns using grafts or flaps</td>
</tr>
<tr>
<td></td>
<td>Otoplasty</td>
<td>Surgical correction of protruding ears</td>
</tr>
<tr>
<td></td>
<td>Brow lift</td>
<td>Surgical procedure to lift low brows</td>
</tr>
<tr>
<td>Face</td>
<td>Rhytidectomy</td>
<td>Surgical procedure to reduce wrinkling and sagging of the face and neck; “face lift”</td>
</tr>
<tr>
<td></td>
<td>Blepharoplasty</td>
<td>Surgical procedure to shape or modify the appearance of eyelids by removing excess eyelid skin ± fat pads</td>
</tr>
<tr>
<td></td>
<td>Rhinoplasty</td>
<td>Intranasal surgical reconstruction of the nose</td>
</tr>
<tr>
<td></td>
<td>Genioplasty</td>
<td>Chin augmentation via osteotomy or synthetic implant to improve contour</td>
</tr>
<tr>
<td></td>
<td>Lip augmentation</td>
<td>Procedure to create fuller lips and to reduce wrinkles around the mouth using collagen injections, fat transferred from other body parts, or implantable materials</td>
</tr>
<tr>
<td>Skin</td>
<td>Chemical peel</td>
<td>Application of one or more exfoliating agents to the skin resulting in destruction of portions of the epidermis and/or dermis with subsequent tissue regeneration</td>
</tr>
<tr>
<td></td>
<td>Dermabrasion</td>
<td>Skin re-surfacing with a rapidly rotating abrasive tool; often used to reduce scars, irregular skin surfaces and fine lines</td>
</tr>
<tr>
<td></td>
<td>Laser resurfacing</td>
<td>Application of laser to the skin which ultimately results in collagen reconfiguration and subsequent skin shrinking and tightening; often used to reduce scars and wrinkles</td>
</tr>
<tr>
<td></td>
<td>Injectable fillers</td>
<td>An injectable substance is used to decrease frown lines, wrinkles, and nasolabial folds; substances include collagen, fat, hyaluronic acid, and calcium hydroxypatite</td>
</tr>
<tr>
<td>Other</td>
<td>Abdominoplasty</td>
<td>Removal of excess skin and repair of rectus muscle laxity (rectus diastasis); “tummy tuck”</td>
</tr>
<tr>
<td></td>
<td>Breast augmentation</td>
<td>Surgical breast enhancement with silicone or saline implants</td>
</tr>
<tr>
<td></td>
<td>Calf augmentation</td>
<td>Augmentation of calf muscle with implants</td>
</tr>
<tr>
<td></td>
<td>Liposuction</td>
<td>Surgical removal of adipose tissue for body contouring (not a weight loss procedure)</td>
</tr>
<tr>
<td></td>
<td>Mastopexy</td>
<td>Surgical breast lift to elevate breast mound and tighten the skin envelope in ptotic breasts</td>
</tr>
<tr>
<td></td>
<td>Sclerotherapy</td>
<td>Injection with a sclerosant to treat telangiectasias and varicose veins</td>
</tr>
<tr>
<td></td>
<td>Gynecomastia</td>
<td>Excessive development of male mammary glands</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treated with traditional or ultrasound-assisted liposuction</td>
</tr>
</tbody>
</table>
Pediatric Plastic Surgery

Craniofacial Anomalies

Table 29. Pediatric Craniofacial Anomalies

<table>
<thead>
<tr>
<th>Definition</th>
<th>Epidemiology</th>
<th>Clinical Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleft Lip</td>
<td>Failure of fusion of maxillary and medial nasal processes</td>
<td>Classified as incomplete/complete and uni/bilateral</td>
<td>Surgery (3 mo): Milliard, Tennison-Randall, or Fisher subunit repair corrections usually required later on (especially for nasal deformity)</td>
</tr>
<tr>
<td></td>
<td>M:F = 2:1</td>
<td>2/3 cases: unilateral, left-sided, male</td>
<td></td>
</tr>
<tr>
<td>Cleft Palate</td>
<td>Failure of fusion of lateral palatine/median palatine processes and nasal septum</td>
<td>Isolated cleft palate: 0.5 per 1,000 (no racial variation)</td>
<td>Special bottles for feeding</td>
</tr>
<tr>
<td></td>
<td>F &gt; M</td>
<td>Isolated (common in females) in conjunction with cleft lip (common in males)</td>
<td>Speech pathologist</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>Premature fusion of ≥1 cranial sutures</td>
<td>Syndromic – associated with genetic mutation</td>
<td>Multidisciplinary team (including neurosurgery, ENT, genetics, dentistry, pediatrics, SLP)</td>
</tr>
<tr>
<td></td>
<td>Primary – abnormal suture, no known cause</td>
<td>Secondary (to microcephaly, hyperthyroid, rickets, etc.)</td>
<td>The type, timing and procedure are dependent on which sutures (lamdoid, sagittal etc.) are involved.</td>
</tr>
<tr>
<td></td>
<td>This may limit brain growth perpendicular to the suture and cause compensatory growth parallel to the fused suture</td>
<td>Dx: irregular head shape, craniofacial abnormalities, x-ray</td>
<td>Early surgery prevents secondary deformities</td>
</tr>
<tr>
<td></td>
<td>1 in 2,000 live newborns; M:F = 52:48</td>
<td></td>
<td># ICP is an indication for emergent surgery</td>
</tr>
<tr>
<td></td>
<td>Syndromes include: Crouzon’s, Apert’s, Saethre-Chotzen, Carpenter’s, Pfeiffer’s, Jackson-Weiss and Boston-type syndromes</td>
<td></td>
<td>ICU bed may be required post-surgically</td>
</tr>
</tbody>
</table>

Figure 38. Types of cleft lips and palates

Congenital Hand Anomalies

Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies

<table>
<thead>
<tr>
<th>Classification</th>
<th>Example</th>
<th>Features</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Failure of Formation</td>
<td>Transverse absence (congenital amputation)</td>
<td>At any level (often below elbow/wrist)</td>
<td>Early prosthesis</td>
</tr>
<tr>
<td>Longitudinal absence</td>
<td>Absent humerus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radial deficiency (radial club hand)</td>
<td>Radial deviation</td>
<td>Thumb hypoplasia</td>
<td>Physiotherapy + splinting</td>
</tr>
<tr>
<td>Thumb hypoplasia</td>
<td>Degree ranges from small thumb with all components to complete absence</td>
<td>Depends on degree – may involve no treatment, webspace deepening, tendon transfer, or pollicization of index finger</td>
<td></td>
</tr>
<tr>
<td>Ulnar club hand</td>
<td>Rare, compared to radial club hand</td>
<td>Stable wrist</td>
<td>Splinting and soft-tissue stretching therapies</td>
</tr>
<tr>
<td>Cleft hand</td>
<td>Autosomal dominant</td>
<td>Often functionally normal (depending on degree)</td>
<td>First web space syndactyly release</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Osteotomy/tendon transfer of thumb (if hypoplastic)</td>
</tr>
<tr>
<td>Classification</td>
<td>Example</td>
<td>Features</td>
<td>Treatment</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>------------------------</td>
<td>---------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Failure of Differentiation/</td>
<td>Syndactyly</td>
<td>Fusion of ≥2 digits</td>
<td>Surgical separation before 6-12 mo of age</td>
</tr>
<tr>
<td>Separation</td>
<td></td>
<td>1/3,000 live births</td>
<td>May require a skin graft to cover the fingers</td>
</tr>
<tr>
<td></td>
<td></td>
<td>M:F = 2:1</td>
<td>Usually good result</td>
</tr>
<tr>
<td></td>
<td>Symbrochydactyly</td>
<td>Classified as partial/complete</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Simple (skin only) vs. complex (osseous or cartilaginous bridges)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Camptodactyly</td>
<td>Congenital flexion contracture (usually at the 5th digit)</td>
<td>Early splitting</td>
</tr>
<tr>
<td></td>
<td></td>
<td>especially 5th digit</td>
<td>Valar release</td>
</tr>
<tr>
<td></td>
<td>Clinodactyly</td>
<td>Radial or ulnar deviation</td>
<td>Arthroplasty (rarely)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Often middle phalanx</td>
<td></td>
</tr>
<tr>
<td>Duplication</td>
<td>Polydactyly</td>
<td>Congenital duplication of digits</td>
<td>Amputation of least functional digit</td>
</tr>
<tr>
<td></td>
<td></td>
<td>May be radial (increased in Aboriginals and Asians) or central or ulnar (increased in Blacks)</td>
<td>Usually &gt; 1 yr of age (when functional status can be assessed)</td>
</tr>
<tr>
<td>Overgrowth</td>
<td>Macroductyly</td>
<td>Rare</td>
<td>None (if mild)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Soft tissue/bony reduction</td>
<td></td>
</tr>
<tr>
<td>Undergrowth</td>
<td>Brachyductyly</td>
<td>Short phalanges</td>
<td>Removal of non-functional stumps</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Osteotomies/tendon transfers</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Distraction osteosynthesis</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Phalangeal/free toe transfer</td>
</tr>
<tr>
<td>Constriction Band Syndrome</td>
<td>Brachysyndactyly</td>
<td>Short webbed fingers</td>
<td>As above + syndactyly release</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>i.e. amniotic (annular)</td>
<td>Variety of presentations</td>
<td>Urgent release for acute, progressive edema distal to band in newborn</td>
</tr>
<tr>
<td>Abnormality</td>
<td></td>
<td></td>
<td>Other reconstruction is case-specific</td>
</tr>
<tr>
<td>Generalized Skeletal Abnormality</td>
<td>Achondroplasia,</td>
<td>Variety of presentations</td>
<td>Treatment depends on etiology</td>
</tr>
<tr>
<td></td>
<td>Marfan’s,</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Marfan’s</td>
<td></td>
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</tr>
</tbody>
</table>

**Table 30. American Society for Surgery of the Hand (ASSH) Classification of Congenital Hand Anomalies (continued)**

**References**


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Population Health and Epidemiology

Catherine R. L. Brown, chapter editor
Lindsey Chapman and Meghna Rajaprakash, associate editors
Shany Gertzbein, EBM editor
Dr. Allison Chris and Dr. Katherine Bingham, staff editors

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For more detail on topics covered in this chapter, use this website as a resource: http://phprimer.afmc.ca/
Acronyms

AR attributable risk  LR likelihood ratio  PYLL potential years of life lost
CAS Children’s Aid Society  MHO Medical Health Officer  QALY quality adjusted life years
CBA cost benefit analysis  MOH Medical Officer of Health  Qi quality improvement
CEA cost effectiveness analysis  MMR maternal mortality ratio  RCT randomized controlled trial
CFR case fatality rate  MSSS Material Safety Data Sheets  RR relative risk
CPhO Chief Public Health Officer  NHN number needed to harm  SMR standardized mortality ratio
DALY disability adjusted life years  NNT number needed to treat  SN sensitivity
EMB evidence based medicine  NPV negative predictive value  SP specificity
HC Health Canada  OR odds ratio  TP true positives
FP false positives  PHAC Public Health Agency of Canada  TN true negatives
FN false negatives  PP per protocol analysis  WHMIS Workplace Hazardous Materials Information System
IMR infant mortality ratio  PPV positive predictive value  WHO World Health Organization
ITT intention to treat analysis  PYL potential years of life lost  WSIB Workplace Safety and Insurance Board
UCO low income cut-off

Public Health Context

- see Ethical, Legal, and Organizational Medicine, ELOAM2 Overview of Canadian Healthcare System for the organization of health care in Canada including the legal foundation and historical context

Definitions

- population health
  - health of the population as measured by health status indicators (e.g. life expectancy, low birth weight rates)
  - influenced by: physical, biological, social, environmental, and economic factors; personal health behaviours; health care services
  - refers to the prevailing or desired level of health in the population of a specific country/region/subset of population
  - considered to be more complex than the aggregate health status of individuals within a population

- public health
  - organized collective efforts of society to protect, promote, and restore the health of the public and prevent illness, injury, and premature death
  - refers to the practices, programs, policies, institutions, and disciplines required to achieve the desired state of population health

- epidemiology
  - study of the distribution and determinants of health-related states or events in a specified populations
  - application of this study to the control of health problems

- public health and preventive medicine (formerly called community medicine)
  - the postgraduate study of health and disease in the population or a specified community
  - five-year Royal College specialty training
  - goal: to identify and address health problems and evaluate the extent to which health services and others address these issues (see http://www.royalcollege.ca for more information)

Public Health Services in Canada

Mission: to promote and protect the health of Canadians, and reduce health inequities through leadership, partnership, innovation, and action in public health

- local public health units and services within regional health authorities (in most provinces except Ontario, where local public health units are either autonomous or within local government) provide programs and activities for health protection, promotion, and disease prevention at local and regional levels
- catchment-area populations range from hundreds to thousands of people, covering areas of 15 km² to 1.5 million km²
- the “core functions” of public health include six essential activities:
  1. health protection: ensure safe water, air, and food; advise on food and drug safety regulations; maintain regulatory framework for control of infectious diseases and protection from environmental threats
  2. health surveillance: using routinely collected health data to monitor and predict health events or determinants
  3. disease and injury prevention: reduce risk of infectious disease by investigation, partner notification, and development of preventative and control measures such as immunization programs; reduce preventable illness and injuries by promoting safe, healthy lifestyles
  4. population health assessment: understand the health of communities/specific population to produce better policies and services
  5. health promotion: maintain and improve health through public policy, community-based interventions, active public participation, and advocacy
  6. emergency preparedness and response: planning for natural (e.g. floods, earthquakes) and man-made (e.g. radioactive substances) threats

Preparation for the LMCC

The AFMC Primer on Population Health is the core text for the LMCC and is available as an online resource on the AFMC website (http://phprimer.afmc.ca)

For the LMCC exam, it is recommended that you also read Chapter 15 in Shah CP. Public Health and preventive medicine in Canada, 5th ed. Toronto: Elsevier, 2003

Historical Perspective

Over the last century, Public Health has evolved through three main epidemiological phases:

- Infectious diseases: controlled in the more developed world but an issue in less developed countries (e.g. polio, malaria)
- Chronic diseases: chronic diseases and other noncommunicable conditions have increased morbidity and mortality (e.g. heart disease and cancer due to risk factors and/or exposures)
- Re-emerging infectious diseases: new or re-emerging infections emerge due to unfamiliar or new pathogens, inefficient or inappropriate antibiotic use, travel, and global warming (e.g. HIV, drug resistant TB and malaria)

CPhO of Canada

- Responsible for the PHAC and reports to the Minister of Health
- As the federal government’s lead public health professional, provides advice to the Minister of Health and Government of Canada on health issues
- Collaborates with other governments, jurisdictions, agencies, organizations, and countries on health matters
- Communicates public health information to health professionals, stakeholders, and the public
- In an emergency, such as an outbreak or natural disaster, provides direction to PHAC staff, including medical professionals, scientists, and epidemiologists, as they plan and respond to the emergency

Source: Public Health Agency of Canada.
### Legislation and Public Health in Canada

#### Table 1. Legislation and Public Health in Canada

<table>
<thead>
<tr>
<th>Federal</th>
<th>Provincial</th>
<th>Municipal (Ontario)</th>
</tr>
</thead>
</table>
| • Health Canada  
  • Provides health services to First Nations, Aboriginal peoples, the Canadian military, and veterans  
  • Approves new drugs and medical devices  
  • Canadian Food Inspection Agency  
  • Monitors food products  
  • Deals with animal-related infections  
  • Regulates food labeling  
  • Public Health Agency of Canada (main Government of Canada agency responsible for public health)  
  • An independent body created to strengthen public health capacity  
  • Focuses on preventing chronic diseases, preventing injuries, and responding to public health emergencies and infectious disease outbreaks  
  • Oversees immigration screening, protects Canadian borders (e.g. airport health inspection)  
  • Liases with the World Health Organization (WHO) on global health issues | • Legislation is in the form of Acts and Regulations  
  • Each province has its own Public Health Act or equivalent (e.g. the Health Protection and Promotion Act in Ontario)  
  • Designates the creation of geographic areas for the provision of public health services  
  • Gives powers to the Chief Medical Officer of Health to control public health hazards  
  • Specifies infectious diseases to be reported to public health units by physicians, laboratories, and hospitals (see Appendix, PH25)  
  • Has the ability to mandate programs that address public health issues, environmental health, and chronic disease prevention | • Local boards of health deliver programs mandated by provincial and municipal or regional legislation  
  • Boards of health are responsible for the delivery of most public health services, such as:  
  • Infectious disease control, including the follow-up of reported diseases and management of outbreaks  
  • Inspection of food premises including those in hospitals, nursing homes, and restaurants  
  • Family health services including pre-conception, preschool, school-aged, and adult health programs  
  • Tobacco control legislation enforcement  
  • Assessment and management of local environmental health risks  
  • Collection and dissemination of local health status reports  
  • Public dental health services to children  
  • By-laws may be approved by municipal governments to facilitate public health issues |

### Concepts of Health

- **wellness**: state of dynamic physical, mental, social, and spiritual well-being that enables a person to achieve full potential and have an enjoyable life  
- **disease**: abnormal, medically-defined changes in the structure or function of the human body  
- **illness**: an individual’s experience or subjective perception of a lack of physical or mental well-being and consequent inability to function normally in social roles  
- **illness behaviour**: an individual’s actions in response to their illness, including whether they seek health care and whether they comply with the subsequent recommendations  
- **sickness**: socially and culturally held conceptions of health conditions that may influence how the patient reacts  
- **impairment**: any loss or abnormality of psychological, physiological, or anatomical structure or function  
- **disability**: any restriction or lack of ability to perform an activity within the range considered normal for a human being  
- **handicap**: the disadvantage for an individual arising due to impairment and disability  
  - limits or prevents the fulfillment of an individual’s normal role as determined by society and depends on age, sex, social, and cultural factors  
  - changes the individual’s relationship with the physical and social environment  
- **health equity**: when all people have “the opportunity to attain their full health potential” and no one is “disadvantaged from achieving this potential because of their social position or other socially determined circumstance.” Differs from health equality. Health inequities are those which are considered unjust and/or avoidable  
- **health equality**: defined as where populations have equal or similar health status. Health inequalities are systematic differences in health status that occur among population groups

### Determinants of Health

- **1974**: the Honourable Marc Lalonde, federal Minister of Health, presented the health field concept entitled *A New Perspective on the Health of Canadians* which included four areas that interact to determine health: human biology, environment, lifestyle, and health care. This concept has been expanded to include numerous determinants of health

**Definitions of Health**

- First multidimensional definition of health, as defined by the WHO in 1948: “state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”  
- WHO updated the definition (socio-ecological definition) of health in 1986: “The ability to identify and to realize aspirations, to satisfy needs, and to change or cope with the environment. Health is therefore a resource for everyday life, not the objective of living. Health is a positive concept emphasizing social and personal resources, as well as physical capacities” (Ottawa Charter for Health Promotion)  
- Other definitions of health have since been proposed that incorporate other dimensions of health (e.g. “Health is a social, economic, and political issue and above all a fundamental human right” – The People’s Charter for Health)

**Determinants of Health**

- Income and social status  
- Social support networks  
- Education and literacy  
- Employment and working conditions  
- Social and work environments  
- Physical environment  
- Personal health practices and coping skills  
- Healthy child development  
- Biology, genetics, and epigenetics  
- Health services  
- Gender  
- Culture

Source: Public Health Agency of Canada
Figure 1. Population health model

Vulnerable Populations

Table 2. Health Determinants of Vulnerable Populations

<table>
<thead>
<tr>
<th>Vulnerable Populations</th>
<th>Definition</th>
<th>Psychosocial/ Socioeconomic</th>
<th>Physical Environment</th>
<th>Individual Behaviour</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aboriginal Peoples</td>
<td>Four specific groups: First Nations Status Indians (registered under the Indian Act), non-Status Indians, Métis, and Inuit</td>
<td>Low income Family violence Low education status Unemployment Homelessness Longer length of disability</td>
<td>Crowded housing Inefficient ventilation Environmental toxins (botulism) TB declining but prevalence higher than rest of population</td>
<td>Smoking Substance misuse Excessive gambling Poor nutrition Sedentary lifestyle High BMI Higher risk of suicide</td>
<td>Mental health awareness Aboriginal-specific DM initiatives Substance abuse treatment programs</td>
</tr>
<tr>
<td>Isolated Seniors</td>
<td>Individuals &gt;65 yr</td>
<td>Elder abuse Lack of emotional support Isolation</td>
<td>Low hazard tolerance Institutionalization Mobility issues</td>
<td>Inactivity Polypharmacy Medical comorbidities</td>
<td>Aging in place of choice Falls and injury prevention Mental health promotion Preventing abuse and neglect</td>
</tr>
<tr>
<td>Children in Poverty</td>
<td>Based on Low Income Cut Offs (LICO) LICO is an income threshold below which a family will likely devote a larger share of its income on the necessities of food, shelter and clothing than the average family</td>
<td>Low income Family dysfunction Lack of educational opportunities</td>
<td>Housing availability Unsafe housing Lack of recreational space</td>
<td>Poor supervision Food insecurity High risk behaviours</td>
<td>Improvements in family income most significant Early childhood education</td>
</tr>
<tr>
<td>People with Disabilities</td>
<td>Includes impairments, activity limitations, and participation restrictions</td>
<td>Low income Low education status Discrimination Stigma</td>
<td>Institutionalization Barriers to access Transportation challenges</td>
<td>Substance misuse Poor nutrition Inactivity Dependency for ADLS</td>
<td>Transportation support Multidisciplinary care Unique support for individuals with specific disabilities (e.g. Trisomy 21)</td>
</tr>
<tr>
<td>New Immigrants</td>
<td>Person born outside of Canada who has been granted the right to live in Canada permanently by immigration authorities</td>
<td>Access to community services Cultural perspectives (including reliance on alternative health practices) Exposure to diseases and conditions in country of origin (e.g. smoke from wood fires, incidence of TB, etc.)</td>
<td>Employment, ESL Newcomer Effect (health worsens over time to match that of the general population) Cultural or religious expectations</td>
<td>Women’s health Mental health Infectious diseases (syphilis blood test, CXR, HIV) Dental and vision screening Vaccinations Cancer screening</td>
<td></td>
</tr>
</tbody>
</table>

Social Determinants: Indigenous People’s Health in Canada

- Colonization: subjugation of Indigenous peoples by the Europeans, leading to the loss of lands, cultural practices, and self-government
- Residential schools: placement of children from Indigenous groups in church-run, government-funded schools for the purpose of assimilation, resulting in loss of identity, alienation, and abuse, with long-lasting consequences of higher rates of addictions, abusive relationships, and suicide
- Treaties and Land Claims: inadequate services for those living on reserves leading to poverty and poor quality infrastructure, reflected in disproportionate burden of infectious diseases (e.g. pertussis, Chlamydia, hepatitis, shigellosis)
- Traditional Approach to Healing: restoring balance in the four realms of spiritual, emotional, mental and physical health of a person acting as an individual, as well as a member of a family, community and nation
- Ideas represented by medicine wheel of First Nations peoples, the Learning Blanket of Inuit peoples, and the Metis tree model of Holistic Lifelong Learning
- Contrast to Western medicine focus of treating illness, leading to challenges for practitioners of Western medicine to meet Aboriginal patients’ needs
- National Aboriginal Health Organization (NAHO) offers 8 guidelines on practicing culturally safe health care for Aboriginal patients including need to allow Aboriginal patients access to ceremony, song, and prayer; the need for information and for family support; guidelines for the appropriate disposal of body parts and for handling death

New Immigrants to Canada

- Mandatory medical exams on entry to Canada by a designated medical practitioner:
  - Complete medical examination for all persons of all ages
  - Chest x-ray and report for persons 11 yr of age and over
  - Urinalysis for persons 5 yr of age and over
  - Syphilis serology for persons 15 yr of age and over
  - HIV testing for applicants 15 yr of age and over, as well as for those children who have received blood or blood products, have a known HIV-positive mother, or have an identified risk. An ELISA HIV screening test should be done for HIV 1 and HIV 2
  - Serum creatinine if the applicant has hypertension (resting blood pressure greater than 140/90 mmHg), a history of treated hypertension, DM, autoimmune disorder, persistent proteinuria, or kidney disorder
Table 2. Health Determinants of Vulnerable Populations (continued)

<table>
<thead>
<tr>
<th>Definition</th>
<th>Psychosocial/Socioeconomic</th>
<th>Physical Environment</th>
<th>Individual Behaviour</th>
<th>Population-Specific Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Homeless Persons</td>
<td>An individual who lacks permanent housing</td>
<td>Low income Food insecurity Mental illness</td>
<td>Exposure to temperature extremes Infections such as West Nile Virus</td>
<td>Substance misuse Violence Safe housing Addictions support Mental health</td>
</tr>
<tr>
<td>Refugee Health</td>
<td>Forced to flee country of origin because of a well-founded fear of persecution and given protection by the Government of Canada</td>
<td>Post-traumatic stress disorders Depression Adjustment problems Partial health coverage via Interim Federal Health Program</td>
<td>Diseases and conditions in country of origin (e.g. malaria, TB, onchocerciasis, etc.) Direct and indirect effects of war</td>
<td>Employment ESL Longstanding prior lack of access to health care (chronically neglected problems) Cultural or religious expectations Vaccinations Women’s health Infectious diseases Dental and vision screening Political advocacy</td>
</tr>
<tr>
<td>Refugee claimant: Arrive in Canada and ask to be considered refugee</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: this chart delineates the major challenges faced by each group, but the issues listed are not unique to each population.

Disease Prevention

Natural History of Disease
- course of a disease from onset to resolution
  1. pathological onset
  2. presymptomatic stage: from onset to first appearance of symptoms/signs
  3. clinically manifest disease: may regress spontaneously, be subject to remissions and relapses, or progress to death

Disease Prevention Strategies
- measures aimed at preventing the occurrence, interrupting through early detection and treatment, or slowing the progression of disease/mitigating the sequelae

Table 3. Levels of Disease Prevention

<table>
<thead>
<tr>
<th>Level of Prevention</th>
<th>Goal</th>
<th>Sample Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Protect health and prevent disease onset</td>
<td>Immunization programs (e.g. measles, diphtheria, pertussis, tetanus, polio, see Pediatrics, P3) Smoking Cessation Seatbelt use</td>
</tr>
<tr>
<td>Secondary</td>
<td>Early detection of disease to minimize morbidity and mortality</td>
<td>Mammography Routine Pap smears</td>
</tr>
<tr>
<td>Tertiary</td>
<td>Treatment and rehabilitation of disease to prevent progression and permanent disability</td>
<td>DM monitoring with HbA1c, eye exams, foot exams Medication</td>
</tr>
</tbody>
</table>

Screening (Secondary Prevention)
- presumptive identification (not diagnosis) of unrecognized disease or defect by the application of tests, examinations, or other procedures which can be applied rapidly

- types of screening
  - mass screening: screening all members of a population for a disease (e.g. phenylketonuria (PKU) and hypothyroidism in all newborns)
  - selective screening: screening of a specific subgroup of the population at risk for a disease (e.g. mammography in women >50 yr old)
  - multiphasic screening: the use of many measurements and investigations to look for many disease entities (e.g. periodic health exam)

- bias in screening
  - lead-time: time between early diagnosis with screening, and when diagnosis would have been made without screening
  - lead-time bias: over-estimation of survival when the estimate is made from the time of screening, instead of the later time when the disease would have been diagnosed without screening
  - length-time bias: overestimation of the survival time due to the sampling of prevalent as opposed to incident cases
    - selection of prevalent cases will favour the over-inclusion of longer-living cases rather than newly-diagnosed incident cases, some of whom may have short survival times
Figure 2. Lead-time bias

Table 4. Ideal Criteria for Screening Tests

<table>
<thead>
<tr>
<th>Disease</th>
<th>Test</th>
<th>Health Care System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Causes significant suffering and/or death</td>
<td>High specificity and sensitivity</td>
<td>Adequate capacity for reporting, follow-up, and treatment of positive screens</td>
</tr>
<tr>
<td>Natural history must be understood</td>
<td>Safe, rapid, easy, relatively inexpensive</td>
<td>Cost effective</td>
</tr>
<tr>
<td>Must have an asymptomatic stage that can be detected by a test</td>
<td>Acceptable to providers and to population</td>
<td>Sustainable program</td>
</tr>
<tr>
<td>Early detection and intervention must result in improved outcomes</td>
<td>Incidence is not too high or too low</td>
<td>Clear policy guidelines</td>
</tr>
</tbody>
</table>

Table 5. Disease Prevention vs. Health Promotion Approach

<table>
<thead>
<tr>
<th>Disease Prevention</th>
<th>Health Promotion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health = absence of disease</td>
<td>Health = positive and multidimensional concept</td>
</tr>
<tr>
<td>Medical model (passive role)</td>
<td>Participatory model of health</td>
</tr>
<tr>
<td>Aimed mainly at high-risk groups in the population</td>
<td>Aimed at the population in its total environment</td>
</tr>
<tr>
<td>One-shot strategy, aimed at a specific pathology</td>
<td>Diverse and complementary strategies aimed at a network of issues/determinants</td>
</tr>
<tr>
<td>Directive and persuasive strategies enforced in target groups</td>
<td>Facilitating and enabling approaches by incentives offered to the population</td>
</tr>
<tr>
<td>Focused mostly on individuals and groups of subjects</td>
<td>Focused on a person’s health status and environment</td>
</tr>
<tr>
<td>Led by professional groups from health disciplines</td>
<td>Led by non-professional organizations, civic groups, local, municipal, regional, and national governments</td>
</tr>
</tbody>
</table>


Healthy Public Policy
- characterized by an explicit concern for health and equity in all areas of policy and by an accountability for health impact
- main aim: to create a supportive environment to enable people to lead healthy lives, thereby making healthy choices easier for citizens
- government sectors must take into account health as an essential factor when formulating policy and should be accountable for the health consequences of their policy decisions
- methods
  - fiscal: imposing additional costs (e.g. taxes on tobacco and alcohol)
  - legislative: implementing legal deterrents (e.g. smoking bans, legal alcohol drinking age)
  - social: improving health beyond providing universally funded health care (e.g. providing affordable housing)

Source: International Conference on Health Promotion, Adelaide, South Australia (1998)

Behaviour Change
- health education serves to
  - increase knowledge and skills
  - encourage positive behaviour changes and discourage unhealthy choices
- health education is an important component of eliciting behaviour change
- behaviour is a result of three factors
  1. predisposing factors: knowledge, attitude, beliefs, values, intentions
  2. enabling factors: skills, supports
  3. reinforcing factors: health care professionals and the social context of family and community

Health Belief Model (1975)
- behaviours undertaken by individuals in order to remain healthy are a function of a set of interacting beliefs
- beliefs include an individual’s perception of his or her susceptibility to a disease, the severity of the disease, and the benefits and costs of health-related actions
- beliefs are modified by socio-demographic and psychosocial variables

Example of Harm Reduction Strategy
Summary of Findings from the Evaluation of a Pilot Medically Supervised Safer Injection Facility
CMAJ 2006;175:1399-1404
Background: This study discusses the outcomes among a population of illicit injection drug users (IDUs) after initiating a supervised safe injecting facility in Vancouver, September 2003. Legal exemption by the Canadian government was granted such that an evaluation of its results be conducted over a 3 yr period.
Study Population: IDUs of the Vancouver area were allowed to inject previously obtained illicit drugs under the supervision of nurses and physicians. IDUs were offered addiction counseling and supports for appropriate community resources.
A random sample of 670 IDUs was recruited and monitored from Dec 2003-July 2004.
Results: Characteristics of IDUs who used the safe injecting facility included age <30 yr, history of public drug use, homelessness, daily heroin and/or cocaine injection, and recent history of overdose. Mean measures of public order problems were taken 6 wk before and 12 wk after initiation of the safer injection facility. It was found that the mean number of IDUs injecting daily in public, along with the mean number of publically discarded syringes were reduced by approximately half.
Conclusions: Overall it has been found that the safer injecting facility in Vancouver has been successful in attracting IDUs at increased risk of HIV, overdose, and public injection of substances. This has resulted in lower incidences of public drug use, publicly discarded syringes and sharing of needles. Other studies associated with this one have demonstrated that there has been no increase in the drug dealing, drug related crimes, or rates of new IDUs in the area surrounding the safer injecting facility.
- individuals must believe that the action will have positive consequences
- individuals must be in a state of readiness
- behaviour can be stimulated by cues to action, which are specific events that can encourage preventive health decisions and actions (e.g. physician recommendation, public advertising)

- **Stages of Change Model**
  - provides a framework in which the Health Belief Model is applied to facilitating behaviour change (e.g. quitting smoking)

  ![Figure 3. Stages of change model](source)

  **Risk Reduction Strategies**
  - **risk reduction**: lower the risk to health without eliminating it (e.g. avoiding sun to lower risk of skin cancer)
  - **harm reduction**: tolerance of some degree of risk behaviour, while aiming to minimize the adverse outcomes associated with these behaviours (e.g. needle exchange programs)

### Measurements of Health and Disease in a Population

#### MEASURES OF DISEASE RATES

- **Incidence Rate**
  - number of new cases in a population over a defined period of time

- **Prevalence**
  - *total number* of cases in a population over a defined period of time
  - *two forms of prevalence*
    - **point prevalence**: attempts to measure the frequency of all disease at a specific point in time, therefore knowledge of the time of onset of disease is not required
    - **period prevalence**: measure constructed from prevalence at a point in time, plus new cases and recurrences over a defined period of time
  - depends on **incidence rate** and disease duration from onset to termination (cure or death)
  - favours the inclusion of chronic over acute cases and may be used to present a biased picture of the disease
  - prevalence studies are cross-sectional and cannot be used for causal inferences
  - prevalence figures are useful for determining the extent of a disease and can aid in the rational planning of facilities and services

- **Age Standardized Rate**
  - adjustment of the crude rate of a health-related event using a “standard” population
  - standard population is one with a known number of persons in each age and sex group
  - standardization prevents bias which could be made by comparing crude rates from two dissimilar populations (e.g. crude death rates over a number of decades are not comparable as the population age distribution has changed with time)

#### MEASURES OF MORTALITY

- **Life Expectancy**
  - the expected number of years that an individual will live based on standardized death rates for the population
  - usually qualified by country, gender, and age
Crude Death Rate
- mortality rate from all causes of death per 1,000 in the population

Infant Mortality Rate (IMR)
- number of deaths among children under 1 yr of age reported during a given time period divided by the number of live births reported during the same time period and expressed per 1,000 live births per year

Maternal Mortality Rate (MMR)
- number of deaths of women during pregnancy and due to puerperal causes per 100,000 live births per year

Standardized Mortality Rate (SMR)
- the ratio of the observed (actual) number of deaths to the expected number of deaths for a group (e.g. age, race, gender, etc.)
- useful for comparing populations that are significantly different in some aspect (e.g. the causes of death in more and less developed countries)

MEASURES OF DISEASE BURDEN

Potential Years of Life Lost (PYLL)
- calculated for a population using the difference between the actual age at death and a standard/expected age at death
- increased weighting of mortality at a younger age

Disability Adjusted Life Year (DALY)
- quantitative indicator of the burden of diseases that reflects the total amount of disability-free life years lost
- includes loss from premature mortality and loss due to a degree of disability over a specific period of time; these disabilities can be physical or mental

Quality Adjusted Life Year (QALY)
- a value from 0 to 1 assigned to a year of life based on perceived quality of life; a yr in "perfect" health is considered equal to 1 QALY, the value of a year in ill health would be lowered based on the burden of disease
- it is possible to have "states worse than death" for example QALY <0 for extremely serious conditions

For additional rate calculations see Outbreak of Infectious Diseases, PH19

Consult the Public Health Agency of Canada for examples and latest statistics

Epidemiology

Population
- a collection of individuals who share a common trait (most commonly applied to a geographic area but it could be another factor such as ethnic group)

Sample
- a selection of individuals from a population or set of observations
- types
  - random: all are equally likely to be selected
  - systematic: an algorithm is used to select a subset
  - stratified: separate representations of more than one subgroup
  - cluster: grouped in space/time to reduce costs
  - convenience: non-random inclusion, usually volunteers

Sample Size
- sample size contributes to the statistical precision of the observed estimate
- increasing the sample size decreases the probability of type I and type II errors (see Data Analysis, PH14)
Bias
• non-random error leading to a deviation of inferences or results from the truth
• any trend in the collection, analysis, interpretation, publication, or review of data that can lead to conclusions that are systematically different from the truth
  • sampling bias: occurs with the selection of a sample that does not truly represent the population
  • sampling procedures should be chosen to prevent or minimize bias
  • measurement bias: systematic error arising from inaccurate measurements of subjects
  • recall bias: when individuals with a disease are more prone to recalling or believing they were exposed to a possible causal factor than those who are free of disease

Confounder
• a variable that is related to both the exposure and outcome but is not measured or is not distributed equally between groups
• distorts the apparent effect of an exposure or risk because it may not be possible to separate/control for the contribution of a single causal factor to an effect (e.g. late maternal age could be a confounder in an investigation of birth order >4 and risk of developing Trisomy 21)

Interpreting Test Results

<table>
<thead>
<tr>
<th>Disease</th>
<th>Present</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test Result</td>
<td>Positive</td>
<td>TP</td>
</tr>
<tr>
<td></td>
<td>Negative</td>
<td>FN</td>
</tr>
</tbody>
</table>

Sensitivity = TP/(TP+FN)
Specificity = TN/(TN+FP)

Likelihood Ratio (LR)
• Likelihood that a given test result would be expected in a patient with disease compared with the likelihood that the same result would be expected in a patient without disease
• LR+ indicates how much the probability of disease increases if the test is positive
• LR- indicates how much the probability of disease decreases if the test is negative

LR+ = Sensitivity = [TP/(TP+FN)]
1 - Specificity = [FP/(TN+FP)]

LR- = 1 - Sensitivity = [FN/(TP+FN)]
Specificity = [TN/(TN+FP)]

Positive Predictive Value (PPV)
• Proportion of people with a positive test who have the disease

PPV = TP / (TP + FP)

Negative Predictive Value (NPV)
• Proportion of people with a negative test who are free of disease

NPV = TN / (TN + FN)

Advanced Neoplasia

<table>
<thead>
<tr>
<th>Test Result</th>
<th>Present</th>
<th>Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>68</td>
<td>147</td>
</tr>
<tr>
<td>Negative</td>
<td>216</td>
<td>2234</td>
</tr>
<tr>
<td>Total</td>
<td>284</td>
<td>2381</td>
</tr>
</tbody>
</table>

Sensitivity = 68/284 = 23.9%
Specificity = 2234/2381 = 93.8%

LR+ = 0.239
LR- = 1 - 0.938 = 0.81
PPV = 68 / (68 + 147) = 31.6%
NPV = 2234 / (2234 + 216) = 91.2%

Figure 5. Interpreting test results: Practical example using FOBT testing in advanced colon cancer

SPIN: use a Specific test to rule IN a hypothesis. Note that specific tests have very few false positives. If you get a positive test, it is likely a true positive

SNOUT: use a Sensitive test to rule OUT a hypothesis. Note that sensitive tests have very few false negatives. If you get a negative test, it is likely a true negative

Figure 4a. Hypothetical population
Figure 4b. Results of diagnostic test on hypothetical population
Figure 4c. Sensitivity of test (e.g. 24/30 = 80% sensitive)
Figure 4d. Specificity of test (e.g. 56/70 = 80% specific)

Source: Loong TW. Understanding sensitivity and specificity with the right side of the brain. BMJ 2003;327:716-719
Sensitivity
- proportion of people with disease who are correctly identified by having a positive test

Specificity
- proportion of people without disease who are correctly identified by having a negative test

Pre-Test Probability
- an estimate of the likelihood a particular patient has a given disease based on known factors

Post-Test Probability
- a revision of the probability of disease after a patient has been interviewed and examined
- calculation process can be more explicit using results from epidemiologic studies, knowledge of the accuracy of tests, and Bayes' theorem
- the post-test probability from clinical examination is the basis of consideration when ordering diagnostic tests or imaging studies
- after each iteration the resultant post-test probability becomes the pre-test probability when considering new investigations

Effectiveness of Interventions

Effectiveness, Efficacy, Efficiency
- three measurements indicating the relative value (beneficial effects vs. harmful effects) of an intervention
  - efficacy: the extent to which a specific intervention produces a beneficial result under ideal conditions
    - ideally, based on the results of a randomized control trial (the theoretical impact)
  - effectiveness: measures the benefit of an intervention under usual conditions of clinical care
    - considers both the efficacy of an intervention and its actual impact on the real world, taking into account access to the intervention, whether it is offered to those who can benefit from it, its proper administration, acceptance of intervention, and degree of adherence to intervention
  - efficiency: a measure of economy of an intervention with known effectiveness
    - considers the optimal use of resources (e.g. money, time, personnel, equipment, etc.)

\[
\begin{array}{ccc}
\text{Disease (e.g. lung CA)} & \\
\text{Exposure (e.g. smoking)} & \text{Present} & \text{Absent} & \text{Total} \\
\text{Present} & A & B & A + B \\
\text{Absent} & C & D & C + D \\
\text{Total} & A + C & B + D & A + B + C + D \\
\end{array}
\]

Case-Control Study
\[
\text{odds ratio (OR)*} = \frac{A \times C}{B \times D} = \frac{A \times D}{B \times C}
\]

Cohort Study
\[
\text{incidence rate of health outcome in exposed} = \frac{C}{C + D} = \text{incidence rate of health outcome in non-exposed}
\]
\[
\text{relative risk (RR)**} = \frac{A}{A + B} + \frac{C}{C + D}
\]
\[
\text{attributable risk (AR)***} = \frac{A}{A + B} + \frac{C}{C + D}
\]

*Ratio of the odds in favour of the health outcome among the exposed to the odds in favour among the unexposed
**Ratio of the risk of a health outcome among exposed to the risk among the unexposed
***Rate of health outcome in exposed individuals that can be attributed to the exposure

Figure 7. Measures of effect by study type

Figure 6. Fagan’s likelihood ratio nomogram: Practical example using PSA levels to calculate post-test probability of prostate cancer


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Equations to Assess Effectiveness
- CER = control group event rate
- EER = experimental group event rate
- RR = EER/CER
- AR = CER – EER
- NNT = 1/ARR

Beware
Do not be swayed by a large RR, as it may appear to be large if event rate is small to begin with. In these cases AR is more important (e.g. a drug which lowers an event which occurs in 0.1% of a population to 0.05% can boast a RR of 50%, and yet the AR is only 0.05%, which is not nearly as impressive)
**Number Needed to Treat (NNT)**
- number of patients who need to be treated to achieve one additional favourable outcome
- only one of many factors that should be taken into account in clinical or health system decision making (e.g. must take into account cost, ease, feasibility of intervention)
  - a condition with death as a potential outcome can have a higher NNT (and be acceptable), as compared to an intervention to prevent an outcome with low morbidity, in which a low NNT would be necessary

**Number Needed to Harm (NNH)**
- number of patients who, if they received the experimental treatment, would lead to one additional patient being harmed, compared with patients who received the control treatment

**Adherence (formerly compliance)**
- degree to which a patient follows a treatment plan

**Coverage**
- extent to which the services rendered cover the potential need for these services in a community

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**Types of Study Design**

### Qualitative vs. Quantitative

<table>
<thead>
<tr>
<th>Qualitative</th>
<th>Quantitative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generates hypothesis (Why? What does it mean?)</td>
<td>Tests hypothesis (What? How much/many?)</td>
</tr>
<tr>
<td>Inductive (specific to general): “bottom up” Observation → pattern → tentative hypothesis → theory</td>
<td>Deductive (general to specific): “top down” Theory → hypothesis → observation → confirmation</td>
</tr>
<tr>
<td>Sampling approach to obtain representative coverage of ideas or concepts</td>
<td>Sampling approach to obtain representative coverage of people in the population</td>
</tr>
<tr>
<td>Narrative: rich, contextual, and detailed information from a small number of participants</td>
<td>Numeric: frequency, severity, and associations from a large number of participants</td>
</tr>
</tbody>
</table>

Source: Adapted from http://phprimer.afmc.ca

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**Quantitative Research Methods**

![Figure 8. Quantitative study designs](Source: Adapted from http://phprimer.afmc.ca)
Observational Study Designs

- observational studies involve neither the manipulation of the exposure of interest nor randomization of the study subjects
- there are two main subtypes of observational studies: descriptive and analytic studies

Descriptive Studies

- describe the events and rates of disease with respect to person, place and time and to estimate disease frequency and time trends
- first sets of studies and are used to generate an etiologic hypothesis, not test a hypothesis

Analytic Studies

- observational studies used to test a specific hypothesis
- includes ecological studies, cohort studies, case-control studies, and cross-sectional studies

Table 7. Observational Study Designs

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Ecological</th>
<th>Cross-Sectional</th>
<th>Case-Control</th>
<th>Cohort</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definition</strong></td>
<td>Units of analysis are populations or groups of people, rather than individuals</td>
<td>Assessment of individuals with respect to presence and absence of exposures and diseases at the same point in time</td>
<td>Samples a group of people who already have a particular outcome (cases) and compares them to a similar sample group without that outcome (controls)</td>
<td>Subjects are sampled and, as a group, classified on the basis of presence or absence of exposure to a particular risk factor</td>
</tr>
<tr>
<td><strong>Subjects</strong></td>
<td>Population (e.g. geographic areas)</td>
<td>Population (sample)</td>
<td>Two study sample populations are compared: cases and controls</td>
<td>One or more cohorts Cohort: group of people with common characteristics (e.g. year of birth) Divided into measured exposed vs. non-exposed groups</td>
</tr>
<tr>
<td><strong>Methods</strong></td>
<td>Descriptions of the average exposure or risk of disease for a population</td>
<td>Collect information from each person at one particular time Tabulate the numbers in groups (e.g. by presence or absence of disease/factor of interest) Make 2 x 2 table and compare groups Estimate prevalence</td>
<td>Ask cases and controls about exposures Select all the cases of a specific disease during a specific time frame Representative of spectrum of clinical disease Select control(s) Represent the general population To minimize risk of bias, may select more than one control group and/or match controls to cases (e.g. age, gender) Association can be concluded between the risk factor and the disease (odds ratio) Estimate incidence</td>
<td>Subjects are followed for a specific period of time to determine development of disease in each exposure group Prospective: measuring from the exposure to the future outcomes – looking forward Retrospective: measuring from outcomes to possible risk factors or protective factors – looking back Collect information on factors from all persons at the beginning of the study Tabulate the number of persons who develop the disease or other measured outcomes of morbidity Provides estimates of incidence, relative risk, attributable risk</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Quick, easy to do Uses readily available data Generates hypothesis</td>
<td>Determines association between variables Quick and uses limited resources Surveys with validated questions allows comparison between studies</td>
<td>Used when disease in population is rare (less than 10% of population) due to increased efficiency Less costly and time consuming</td>
<td>Shows an association between a factor and an outcome/several outcomes Stronger evidence for causation</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>Poor generalizability to individual level (not direct assessment of causal relationship) Ecological fallacy: an incorrect inference about individuals in the population</td>
<td>Does not allow for assessment of temporal relationship or causation between variables Recall bias (see Bias, PH9)</td>
<td>Recall bias (see Bias, PH9) Confounding Selection bias for controls Only one outcome can be measured</td>
<td>By itself, cannot establish causation Confounding factors are common as the cohort self-selects the exposure, or unknown/unmeasured factors are associated with the measured exposure Cost and duration of time needed to follow cohort</td>
</tr>
<tr>
<td><strong>Examples</strong></td>
<td>A study looking at the association between smoking rates and lung cancer rates in different countries at the population level without individual data on both factors</td>
<td>A study that examines the distribution of BMI by age in Ontario at a particular point in time</td>
<td>A famous case control study is by Sir Richard Doll who demonstrated the link between tobacco smoking exposure and lung cancer cases at the individual level</td>
<td>A famous cohort study is the Framingham Heart Study, which assessed the long-term cardiovascular risks of diet, exercise, medications such as ASA, etc.</td>
</tr>
</tbody>
</table>
Experimental Study Designs

• not discussed here are non-randomized control trials (e.g. allocation by clinic or other non-random basis – performed when randomization is not possible) and clinical trials (e.g. test treatments or laboratory tests in human subjects)

RANDOMIZED CONTROLLED TRIAL (RCT)

Definition
• subjects are assigned by random allocation to two or more groups, one of which is the control group, the other group(s) receive(s) an experimental intervention

Subjects
• individuals are separated into groups by a random process to ensure as much as possible equal distribution of known and unknown factors except for the experimental exposure (e.g. the treatment)

Methods
• random allocation of individuals into two or more treatment groups through a centralized concealed process
• method of assessment to reduce bias
  ▪ single-blind: subject does not know group assignment (intervention or placebo)
  ▪ double-blind: subject and observer both unaware of group assignment
  ▪ triple-blind: subject, observer, and analyst unaware of group assignment (rarely done)
• one group receives placebo or standard therapy
• one or more groups receive(s) the intervention(s) under study
• the outcome is measured and the groups are compared
• all other conditions are kept the same between groups

Advantages
• “gold standard” of studies, upon which the practice of EBM is founded
• provides the strongest evidence for effectiveness of intervention
• with sufficient sample size and appropriate randomization, threats to validity are minimized
• allows prospective assessment of the effects of intervention while minimizing bias

Disadvantages
• some exposures are not amenable to randomization (e.g. cannot randomize subjects to poverty/wealth or to harmful exposures such as smoking) due to ethical or feasibility concerns
• difficult to randomly allocate groups (e.g. communities, neighbourhoods)
• difficult to study rare events, since RCTs would require extremely large sample sizes
• costly

Summary Study Designs

META-ANALYSIS

Definition
• a form of statistical analysis that combines the results of independent studies addressing a common research hypothesis, as identified through systematic review, into one large study

Subjects
• combination of all the subjects used in original studies

Methods
• selection of relevant studies from the published literature which meet quality criteria
• statistical models used to combine the results of each independent study
• provides a summary statistic of overall results as well as graphic representation of included studies

Advantages
• attempts to overcome the problem of reduced power due to small sample sizes of individual studies
• ability to control for inter-study variation

Disadvantages
• sources of bias may not be controlled for
• reliance on published studies may increase the potential conclusion of an effect as it can be difficult to publish studies that show no significant results (publication bias)
• the decision to include/reject a particular study is subjective
Methods of Analysis

Distributions

- distribution describes the probability of events
- normal (Gaussian) or non-normal (skewed, bimodal, etc.)
- characteristics of the normal distribution
  - mean = median = mode
  - 67% of observations fall within one standard deviation of the mean
  - 95% of observations fall within two standard deviations of the mean
- measures of central tendency
  - mean: sum of all observations divided by total number of variables
  - median: value at the 50th percentile, a better reflection of the central tendency for a skewed distribution
  - mode: most frequently observed value in a series
- measures of dispersion
  - range: the largest value minus the smallest value
  - variance: a measure of the spread of data
  - standard deviation: the average distance of data points from the mean (the positive square root of variance)
- given the mean and standard deviation of a normal or binomial distribution curve, a description of the entire distribution of data is obtained

Data Analysis

Statistical Hypotheses

- null (H₀)
  - no relationship exists between the two stated variables (i.e. no association between the hypothesized exposure and the outcome)
- alternative (H₁)
  - a relationship does exist between the two stated variables

Type I Error (α Error)

- the null hypothesis is falsely rejected (i.e. concluding an intervention X is effective when it is not, or declaring an observed difference to be real rather than by chance)
- the probability of this error is denoted by the p-value
- studies tend to be designed to minimize this type of error, since a type I error can have larger clinical significance than a type II error

Type II Error (β Error)

- the null hypothesis is falsely accepted (i.e. stating intervention X is not effective when it is, or declaring an observed difference/effect to have occurred by chance when it is present)
- higher level of error is acceptable for most studies
- can also be used to calculate statistical power

Power

- probability of correctly rejecting a null hypothesis when it is in fact false (i.e. the probability of finding a specified difference to be statistically significant at a given p-value)
- power increases with an increase in sample size
- power = 1 – β, and is therefore equal to the probability of a true positive result

Statistical Significance

- the probability that the statistical association found between the variables is due to random chance alone (i.e. that there is no association)
- the preset probability is set sufficiently low that one would act on the result; frequently p=0.05
- when statistical tests result in a probability less than the preset limit, the results are said to be statistically significant (i.e. p<0.05)

Clinical Significance

- measure of clinical usefulness (e.g. 1 mmHg BP reduction may be statistically significant, but may not be clinically significant)
- depends on factors such as cost, availability, patient compliance, and side effects in addition to statistical significance

Trend

- an observed directional relationship that does not meet criteria for statistical significance and thus should be interpreted with caution
Confidence Interval (CI)
- provides a range of values within which the true population result (e.g., the mean) lies
- frequently reported as 95% CI (i.e., one can be 95% certain that the true value is within this data range)
- bounded by the upper and lower confidence limits

Data
- information collected from a sample of a population
- there are 2 overall classes of data listed with examples
  - discrete
    - categorical (e.g., gender, marital status)
    - ordinal (e.g., low, medium, high)
  - continuous (e.g., serum cholesterol, hemoglobin, age)

Accuracy
- how closely a measurement approaches the true value

Reliability
- how consistent a measurement is when performed by different observers under the same conditions or by the same observer under different conditions

Validity
- extent to which a measurement approaches what it is designed to measure
- determined by the accuracy and reliability of a test

Internal Validity
- degree to which the findings of the sample truly represent the findings in the study population
- dependent on the precision and accuracy

External Validity (i.e., Generalizability)
- degree to which the results of the study can be generalized to other situations or populations

Common Statistical Tests

Table 8. Statistical Tests

<table>
<thead>
<tr>
<th>What are you trying to show?</th>
<th>Z-Test (known as t-test for samples &lt;30)</th>
<th>Analysis of Variance (ANOVA)</th>
<th>Chi-Squared Test ($\chi^2$)</th>
<th>Linear Regression</th>
<th>Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compare the mean values of an outcome variable between two groups (e.g., difference in average BP between men and women)</td>
<td>Compare the mean values of an outcome variable between two or more groups (e.g., difference in average BP between persons in three towns)</td>
<td>Test the correspondence between a theoretical frequency distribution and an observed frequency distribution (e.g., if one sample of 20 patients is 30% hypertensive and another comparison group of 25 patients is 60% hypertensive, a chi-squared test determines if this variation is more than expected due to chance alone)</td>
<td>Looks at associations between two or more continuous variables (e.g., age and blood pressure)</td>
<td>Shows how a change in one explanatory variable affects the status (e.g., ill vs. non-ill) of the outcome variable</td>
<td></td>
</tr>
</tbody>
</table>

What kind of data do you have in your study?

<table>
<thead>
<tr>
<th>Data on two groups</th>
<th>Mean of groups (one or more) Overall mean of an entire sample</th>
<th>Data on two or more populations and two or more outcome measures</th>
<th>Data on at least one population</th>
<th>Data on at least one population</th>
</tr>
</thead>
</table>

What kind of variables do you measure?

<table>
<thead>
<tr>
<th>Dependent Variable</th>
<th>Continuous data</th>
<th>Continuous data</th>
<th>Categorical (2 or more)</th>
<th>Continuous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent Variable</td>
<td>Categorical (2 only)</td>
<td>Categorical (2 or more)</td>
<td>Categorical (2 or more)</td>
<td>Continuous</td>
</tr>
</tbody>
</table>

Assumptions

| “Normal” distribution | None | Dependent variable has “normal” distribution Linear relationship between variables | None |

Figure 12. Accuracy vs. reliability

A wider confidence interval implies more variance than a tighter confidence interval
Causation

Criteria for Causation (Sir Bradford Hill)
1. **strength of association**: the frequency with which the factor is found in the disease and the frequency with which it occurs in the absence of disease
2. **consistency**: is it the same outcome with different populations or study design?
3. **specificity**: is the association particular to your intervention and measured outcome?
4. **temporal relationship**: did the exposure occur before the onset of the disease?
5. **biological gradient**: finding a quantitative relationship between the factor and the frequency (e.g. dose response relationship)
6. **biological plausibility**: does the association/causation make biological sense?
7. **coherence**: can the relationship be explained/accounted for based on what we know about the laws of science, logic, etc.?
8. **experimental evidence**: experiment that investigates what happens when the suspected offending agent is removed (e.g. is there improvement?)
9. **analogy**: do other established associations provide a model for this type of the relationship?

**Note**: Not all criteria must be fulfilled to establish scientific causation, and the modern practice of EBM emphasizes 'experimental evidence' as superior to other criteria for experimental causation review. However many causation questions in health cannot be answered with experimental methods.

Assessing Evidence

- critical appraisal is the process of systematically examining research evidence to assess validity, results, and relevance before using it to inform a decision
# Health Services Research

## Continuous Quality Improvement

**Quality Improvement (QI)**
- method of evaluating and improving processes; focusing more on systems and systematic biases, which are thought to be the cause of variation in quality, as opposed to individuals
- taking measures to increase efficiency of action with the purpose of achieving optimal quality

**Quality Assurance**
- management system to assure the quality of health care provided by workers and received by patients
- constantly aims to improve standards and the frequency of attaining those standards
- **five-stage process of quality assurance**
  1. establishment of functional goals
  2. implementation of procedures to achieve those goals
  3. regular assessment of performance relative to the goals
  4. proposal of solutions to close the gap between performance and goals
  5. documentation and reporting of this assessment activity

**Quality Control**
- method of maintaining standards by reviewing the quality of all factors involved in the process

**Continuous Quality Improvement**
- management approach to improve and maintain quality via continuous assessment of potential defects, followed by action to improve process, avoid decrease in quality or correcting process in early stages
- continuous feed-forward process

**Quality Management**
- encompasses quality assurance, quality control, and quality improvement to achieve consistent quality

**Total Quality Management**
- management philosophy for improving quality while controlling costs
- focusing on the system rather than the individual, to ensure decisions are made to support quality and remove barriers to quality inherent in bureaucratic, hierarchical systems

**Audit**
- process of systematic examination of a quality system carried out by internal or external quality auditors
- to determine whether quality processes and results comply with goals, and whether processes have been implemented effectively

**Systems Analyses Tools**
1. 5 Whys: brainstorming to simplify the process of change; continue asking ‘why’ until the root of the problem is discovered
2. Ishikawa Diagrams (i.e. Fishbone Diagrams): identify generic categories of problems that have an overall contribution on the effect

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**Levels of Evidence: Classifications Cited in Guidelines/Consensus Statements**

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>based on RCTs (or meta-analysis of RCTs) big enough to have low risk of incorporating FP or FN results</td>
</tr>
<tr>
<td>II</td>
<td>based on RCTs too small to provide Level I evidence; may show positive trends that are non-significant, or have a high risk of FN results</td>
</tr>
<tr>
<td>III</td>
<td>based on non-randomized, controlled or cohort studies; case series; case-controlled; or cross-sectional studies</td>
</tr>
<tr>
<td>IV</td>
<td>based on opinion of respected authorities or expert committees, as published consensus conferences/guidelines</td>
</tr>
<tr>
<td>V</td>
<td>opinions of the individuals who have written-reviewed the guidelines (i.e. Level IV evidence), based on experience/knowledge of literature/peer discussion</td>
</tr>
</tbody>
</table>

**Canadian Task Force on Preventive Health Care Grading of Health Promotion Actions**

A: Good evidence to recommend the preventive health measure
B: Fair evidence to recommend the preventive health measure
C: Existing evidence is conflicting and does not allow making a recommendation for or against use of the clinical preventive action, however other factors may influence decision-making
D: Fair evidence to recommend against the preventive health measure
E: Good evidence to recommend against the preventive health measure
I: Insufficient evidence (in quantity and/or quality) to make a recommendation, however other factors may influence decision-making

Source: Canadian Task Force on Representative Health Care. Canadian task force on preventive new grades for recommendations CMAJ 2003;169:207-208
3. **Defect check sheets**: consider all defects and tally up the number of times the defect occurs

4. **Pareto Chart**: x vs. y chart; x-axis = defect categories, y-axis = frequency; plot cumulative frequency on the right y-axis
   - Purpose is to highlight most important among large set of factors contributing to defects/poor quality

### Precede-Proceed Model
- Tool for designing, implementing, and evaluating health interventions/programs

<table>
<thead>
<tr>
<th>PRECEDE Phase</th>
<th>PROCEED Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 – Identify the ultimate desired result</td>
<td>Phase 5 – Implementation (design and conduct the intervention)</td>
</tr>
<tr>
<td>Phase 2 – Identify and set priorities among health issues and their behavioural and environmental determinants</td>
<td>Phase 6 – Process Evaluation (determine if the program is implemented as planned)</td>
</tr>
<tr>
<td>Phase 3 – Identify the predisposing, enabling, and reinforcing factors that affect the behaviours and environmental determinants</td>
<td>Phase 7 – Impact Evaluation (measure intermediate objectives – predisposing, enabling, and reinforcing factors)</td>
</tr>
<tr>
<td>Phase 4 – Identify the administrative and policy factors that influence what can be implemented</td>
<td>Phase 8 – Outcome Evaluation (measure desired result)</td>
</tr>
</tbody>
</table>

### Cost Analysis

**Cost Benefit Analysis (CBA)**
- A process of, either explicitly or implicitly, weighing the total expected costs against the total expected benefits of one or more actions in order to choose the best or most profitable option
- All costs are adjusted for the time value of money so that costs that may change over time are expressed on a common basis in terms of their present value

**Cost Effectiveness Analysis (CEA)**
- A comparison of the relative expenditure (costs) and outcomes (effects) of two or more courses of action
- Cost effectiveness analysis is often used where a full cost benefit analysis is inappropriate
- A CEA is commonly expressed in terms of a ratio: the denominator is a gain in health from a measure (e.g., years of life, premature births averted, sight-years gained) and the numerator is the cost of the health gain
- The most commonly used outcome measure is quality-adjusted life years (QALY) (see Quality Adjusted Life Year, PH8)
Outbreak of Infectious Diseases

Definitions

Endemic
- constant presence of disease or infectious agent in a given geographic area or population subgroup (i.e. usual rate of disease)

Outbreak
- occurrence of new cases clearly in excess of the baseline frequency of the disease in a defined community or population over a given period of time
- synonymous with epidemic, although generally considered to be an epidemic that is localized, has an acute onset, or is relatively short in duration

Epidemic
- any disease, infectious or chronic, occurring at a greater frequency than usually expected in a defined community or institutional population over a given time period (i.e. excessive rate of disease)

Pandemic
- epidemic over a wide area, crossing international boundaries, and affecting a large number of people

Attack Rate
- cumulative incidence of infection within a defined group observed during a specific period of time in an epidemic
- calculated by dividing the total number of people who develop clinical disease by the population at risk, usually expressed as a percentage

Secondary Attack Rate
- number of cases among contacts occurring within the incubation period following exposure to the primary case, in relation to the total exposed contacts
- infectiousness reflects the ease of disease transmission and is usually measured by the secondary attack rate

Virulence
- severity of the disease produced by the organism in a given host
- expressed as the ratio of the number of cases of severe and fatal infection to the total number of clinically affected

Case-Fatality Rate (CFR)
- proportion of individuals contracting a disease who die as a result of that disease
- most frequently applied to a specific outbreak of acute disease in which all patients have been followed for an adequate period of time to include all attributable deaths
- must be clearly differentiated from the mortality rate

Mortality Rate/CRude Death Rate
- estimation of the portion of the population that dies during a specified period from all causes of death

Steps to Control an Outbreak

1. Define the Problem
   - is it an outbreak?

2. Appraise Existing Data and Institute a Surveillance System
   - case definition: formulated from the most common symptoms or signs; definition includes the likely date of onset of illness of the first case (e.g. any person with onset of fever higher than 38.5°C and cough within past 28 d)
- active surveillance: identify those who may have been exposed to the infectious agent and who fit the case definition through active efforts, including
  - contacting emergency rooms, physicians’ offices, local schools
  - obtaining records from health units, such as mortality or laboratory records

Infection Control Precautions
(see Infectious Diseases, ID6)
- Contact (impetigo, chicken pox, warts)
  - Wash hands
  - Gloves
  - Gown
  - Wipe equipment after use
- Airborne (TB)
  - Contact precautions PLUS
  - N95 mask (fit tested)
  - Negative pressure room
- Droplet (influenza, mumps, pneumonia)
  - Contact precautions PLUS
  - Goggles/face shield
  - Surgical mask


Active Surveillance
Outreach such as visits or phone calls by the public health/surveillance authority to detect unreported cases (e.g. an infection control nurse goes to the ward and reviews temperature charts to see if any patient has a nosocomial infection)

Passive Surveillance
A surveillance system where the public health/surveillance authority depends on others to submit standardized forms or other means of reporting cases (e.g. ward staff notify infection control when new cases of nosocomial infections are discovered)
3. Formulate Hypotheses and Implement Initial Control Measures
- track outbreak evolution to develop hypotheses about potential source and populations at risk
- case management depends on symptoms, suspected agent, population at risk, and location
- population management requires public health services in the community and infection control teams in hospitals to initiate initial control measures:
  - disseminate information about risk reduction
  - ensure adherence to personal preventative measures (e.g. hand hygiene, personal protective equipment)
  - prevent new cases (e.g. vaccination, post-exposure prophylaxis)
  - decrease risk of propagation (e.g. quarantine)
  - treat existing cases (e.g. antibiotics, antivirals, supportive care)

4. Test the Hypothesis through Analysis of Surveillance Data or Special Studies
- analyze outbreak surveillance data
- generate epidemic curves
  - usually a frequency histogram, with the number of cases plotted on the vertical axis and dates or times of onset along the horizontal axis
  - curve can indicate whether the epidemic (outbreak) has a common source or whether it is propagated
  - **point source epidemic**: exposure is brief and essentially simultaneous
  - **extended source epidemic**: exposure lasts for a period of days to weeks and may be continuous (no irregular peaks) or intermittent (irregularly spaced peaks)
  - **propagated epidemic**: begins with only a few exposed persons but is maintained by person-to-person transmission (e.g. measles/influenza); epidemic curve shows a series of peaks
- use epidemic curves, cross-sectional studies, and/or case-control studies to evaluate hypotheses about cause of outbreak

5. Draw Conclusions and Re-Adjust Hypothesis and Control Measures
- establish cause of outbreak with further epidemiologic investigation and revise initial control measures accordingly

6. Plan for Long-Term Prevention and Control
- implement prevention measures to avoid similar future incidents
  - strengthen resistance of hosts (e.g. immunization)
  - interrupt modes of transmission in environment (e.g. improvements in food processing)
  - communicate outbreak prevention and control strategies to the public


**Infection Control Targets**
- interventions should target host, agent, environment, and their interactions
Environmental Health

**Definition**
- study of conditions in the natural and human-made environment that influence human health and well-being
- environmental exposures
  - four common hazards: chemical, biological, physical, and radiation
  - four main reservoirs: air, food, water, and soil
  - three main routes: inhalation, ingestion, or absorption (skin)
  - usually divided into two main settings
    - workplace (including schools): may see high level exposure in healthy individuals (see *Occupational Health*, PH23)
    - non-workplace: generally low level but chronic exposure; population at risk includes extremes of age, developing fetuses, and ill or immunocompromised individuals
- health impacts of the environment also include factors such as urban planning and how individuals interact with the built environment (e.g. safe pedestrian and bicycle paths are neighbourhood features that can facilitate more active lifestyles among residents)

**Environmental Health Jurisdiction**

<table>
<thead>
<tr>
<th>Public Health Unit</th>
<th>Enforcement of water and food safety regulations (including restaurant food safety)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sanitation</td>
</tr>
<tr>
<td></td>
<td>Assessment of local environmental risks</td>
</tr>
<tr>
<td></td>
<td>Monitoring and follow-up of reportable diseases</td>
</tr>
<tr>
<td>Municipal Government</td>
<td>Waste disposal</td>
</tr>
<tr>
<td></td>
<td>Recycling</td>
</tr>
<tr>
<td></td>
<td>Water and sewage treatment/collection/distribution</td>
</tr>
<tr>
<td>Provincial and Territorial Government</td>
<td>Water and air quality standards</td>
</tr>
<tr>
<td></td>
<td>Industrial emission regulation</td>
</tr>
<tr>
<td></td>
<td>Toxic waste disposal</td>
</tr>
<tr>
<td>Federal Government</td>
<td>Designating and regulating toxic substances</td>
</tr>
<tr>
<td></td>
<td>Regulating food products (e.g. Health Canada)</td>
</tr>
<tr>
<td></td>
<td>Setting policy for pollutants that can travel across provincial boundaries</td>
</tr>
<tr>
<td>International</td>
<td>Multilateral agreements (e.g. Kyoto Protocol, UN Convention on Climate Change, International Joint Commission)</td>
</tr>
</tbody>
</table>

**Risk Assessment**

**Hazard Identification**
- what is the hazard involved?
- assess potential hazards by taking an environmental health history

**Risk Characterization**
- is the identified agent likely to elicit the patient’s current symptoms?
- review known health impacts of the hazard and identify specific properties that contribute to or diminish adverse effects (e.g. evaluate threshold levels)

**Exposure Assessment**
- is the patient’s exposure to the environmental agent sufficient to have caused the current symptoms?
- quantify exposure through direct measurement or by reviewing frequency and nature of contact with hazard

**Air**

**Biological Hazards**
- moulds thrive in moist areas; 10-15% of the population allergic
- bacteria survive as spores and aerosols, can be distributed through ventilation systems (e.g. *Legionella*)
- dust mites (year-round) and pollens (seasonal) can trigger upper and lower-airway symptoms
Chemical Hazards
- ground-level ozone
  - main component of smog with levels increasing in major cities
  - worsens asthma, irritates upper airway
- carbon monoxide (fossil fuel-related, common byproduct of combustion)
  - aggravates cardiac disease at low levels
  - headache, nausea, dizziness at moderate levels
  - fatal at high levels
- sulphur dioxide (fossil fuel-related), nitrogen oxides
  - contribute to acid rain and exacerbate breathing difficulties
- organic compounds at high levels (e.g. benzene, methylene chloride, tetrachloroethylene)
  - tend to be fat-soluble, easily absorbed through skin and difficult to excrete
- heavy metals emissions (e.g. nickel, cadmium, chromium)
  - variety of health effects: upper airway disease, asthma, decreased lung function
- second-hand tobacco smoke
  - respiratory problems, increase risk of lung cancer
  - particulates associated with decreased lung function, asthma, upper airway irritation

Radiation Hazards
- sound waves
  - ionizing radiation
  - radon is naturally produced by soil containing uranium or radium, can contaminate indoor air and is associated with a small proportion of lung cancers
- ultraviolet radiation is increasing due to ozone layer destruction and increases risk of skin cancer
  - non-ionizing radiation
  - visible light, infrared, microwave

Water

Biological Hazards
- mostly due to human and animal waste
- Aboriginal Canadians, rural Canadians at higher risk
- bacteria: Escherichia coli (e.g. Walkerton, ON), Salmonella, Pseudomonas, Shigella
- protozoa: Giardia, Cryptosporidium (e.g. North Battleford, SK)

Chemical/Industrial Hazards
- chlorination by-products (e.g. chloroform can cause cancer at high levels)
- volatile organic compounds, heavy metals, pesticides, and other industrial waste products can be present in groundwater
- fluoride at high levels (greater than that of municipal fluoridation) can cause skeletal fluorosis

Soil

Biological Hazards
- biological contamination: tetanus, Pseudomonas

Chemical Hazards
- contamination sources: rupture of underground storage tanks, use of pesticides and herbicides, percolation of contaminated water runoffs, leaching of wastes from landfills, dust from smelting and coal burning power plants, residue of industrial waste/development (e.g. urban agriculture), lead deposition, leakage of transformers
- most common chemicals: petroleum hydrocarbons, solvents, lead, pesticides, motor oil, other industrial waste products
- health effects
  - infants and toddlers at highest risk of exposure due to hand-mouth behaviours
  - dependent on contaminant: leukemia, kidney damage, liver toxicity, neuromuscular blockade, developmental damage to the brain and nervous system, skin rash, eye irritation, headache, nausea, fatigue

The Walkerton Tragedy
In May 2000, the drinking water system in the town of Walkerton, ON, became contaminated with Escherichia coli O157:H7 and Campylobacter jejuni. Over 2,300 individuals became ill; 27 people developed hemolytic uremic syndrome and 7 individuals died in the outbreak.

Food

Biological Hazards

Table 11. Comparison of Select Biological Contaminants of Food and Effects on Human Health

<table>
<thead>
<tr>
<th>Source</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salmonella</td>
<td>GI symptoms</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Joint pain, GI symptoms</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Watery or bloody diarrhea</td>
</tr>
<tr>
<td>Listeria monocytogenes</td>
<td>Hemolytic uremic syndrome (esp. children)</td>
</tr>
<tr>
<td>Clostridium botulinum</td>
<td>Dizziness, weakness, respiratory failure, GI symptoms: thirst, nausea, constipation</td>
</tr>
<tr>
<td>Prion (BSE*)</td>
<td>Creutzfeldt-Jakob disease</td>
</tr>
</tbody>
</table>

*BSE = bovine spongiform encephalopathy

- other biological food contaminants include
  - viruses, mould toxins (e.g. aflatoxin has been associated with liver cancer), parasites (e.g. Toxoplasmosis, tapeworm), paralytic and shellfish poisoning (rare), genetically modified organisms (controversial as to health risks/benefits)

Chemical Hazards

- many persistent organic pollutants are fat-soluble and undergo bioamplification
- drugs (antibiotics, hormones)
- inadequately prepared herbal medications
- food additives and preservatives
  - nitrates highest in cured meats; can be converted to carcinogenic nitrosamines
  - sulphites commonly used as preservatives; associated with sulphite allergy (hives, nausea, shock)
  - pesticide residues
  - older pesticides (e.g. DDT) have considerable human health effects
  - polychlorinated biphenyls (PCBs)
    - effects (severe acne, numbness, muscle spasm, bronchitis) much more likely to be seen in occupationally exposed individuals than in the general population
- dioxins and furans
  - levels highest in fish and marine mammals, also present in breast milk
  - can cause immunosuppression, liver disease, respiratory disease

Occupational Health

- occupational health is the maintenance and promotion of health in the work environment
- services encompass health promotion and protection (primary prevention), disease prevention (secondary prevention), and treatment and rehabilitation (tertiary prevention)
- general bias towards reporting occupational injuries versus occupational disease, as occupational disease is harder to identify

Taking an Occupational Health History

- current and previous job duties
- exposures
  - identification: screen for chemical, metal, dust, biological, and physical hazards as well as psychological stressors; review relevant workplace MSDS
  - assessment: duration, concentration, route, exposure controls (e.g. ventilation, personal protective equipment)
- temporal relationship: changes in symptoms in relationship to work environment
- presence of similar symptoms in co-workers
- non-work exposures: home, neighbourhood, hobbies

Figure 18. Hierarchy of controls for reduction of occupational exposures

http://www.cdc.gov/niosh/topics/hierarchy/
### Occupational Hazards

**Table 12. Occupational Hazards**

<table>
<thead>
<tr>
<th>Physical</th>
<th>Chemical</th>
<th>Biological</th>
<th>Psychosocial</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Trauma (e.g. fractures, lacerations)</td>
<td>• Organic solvents (e.g. benzene, methyl alcohol; most toxic is carbon tetrachloride)</td>
<td>• Exposure to bacteria, viruses, fungi, protozoa, Rickettsia</td>
<td>• Workload stressors</td>
</tr>
<tr>
<td>• Noise (e.g. hearing loss)</td>
<td>• Mineral dusts (e.g. silica leads to silicosis and predisposition to TB, asbestos leads to diffuse fibrosis and mesothelioma, coal leads to pneumoconiosis)</td>
<td>• Blood should be considered a potentially toxic substance due to blood-borne infectious diseases (e.g. HIV, hepatitis B)</td>
<td>• responsibility</td>
</tr>
<tr>
<td>• Temperature</td>
<td>• Heavy metals (e.g. nickel, cadmium, mercury, lead)</td>
<td>• Consider exposure to disease in endemic countries, travelers from endemic countries, or recent travel history in the setting of acute onset of symptoms (e.g. malaria, SARS, TB)</td>
<td>• fear of job loss</td>
</tr>
<tr>
<td>• heat cramps, heat exhaustion, heat stroke</td>
<td>• Gases (e.g. halogen gases, sulphur dioxide, carbon monoxide, nitrogen oxides)</td>
<td>• Second-hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)</td>
<td>• geographical isolation</td>
</tr>
<tr>
<td>• hypothermia, frostbite</td>
<td>• Second-hand smoke (causal factor for lung cancer, lung disease, heart disease, asthma exacerbations; may be linked to miscarriage)</td>
<td>• Skin diseases (major portion of compensations, e.g. contact dermatitis, occupational acne, pigmentation disorders)</td>
<td>• shift work</td>
</tr>
<tr>
<td>• Air pressure (barotrauma, decompression sickness)</td>
<td>• Radiation</td>
<td></td>
<td>• bullying</td>
</tr>
<tr>
<td>• Ergonomic</td>
<td>• • repetitve use/overuse injuries, excessive force, awkward postures, poorly designed physical work environment</td>
<td>• • non-ionizing: visible light, infrared</td>
<td>• harassment (sexual/non-sexual)</td>
</tr>
<tr>
<td>• • tenosynovitis, bursitis, carpal tunnel syndrome</td>
<td>• • ionizing: UV, x-rays, y rays</td>
<td>• • radiation</td>
<td>• Incurs high cost from absenteeism, poor productivity, mental illness (e.g. post-traumatic stress disorder)</td>
</tr>
<tr>
<td>• Radiation</td>
<td>• • Electricity</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
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</tr>
</tbody>
</table>

### Workplace Legislation

- universal across Canada for corporate responsibility in the workplace: due diligence, application of Workplace Hazardous Materials Information System (WHMIS), existence of joint health and safety committees in the workplace with representatives from workers and management
- jurisdiction in Canada is provincial (90% of Canadian workers), except for 16 federally regulated industries (e.g. airports, banks, highway transport) under the Canada Labour Code
- Ontario’s Occupational Health and Safety Act
  - sets out rights of workers and duties of employers, procedures for dealing with workplace hazards, and law enforcement
  - workers have the right to
    - participate (e.g. have representatives on joint health and safety committees)
    - know (e.g. be trained and have information about workplace hazards)
    - refuse work (e.g. workers can declare tasks they feel are overly dangerous)
    - note: For some occupations, this right is restricted if, for example, danger/risk is normal part of work or refusal would endanger others (e.g. police, firefighters, some health care workers)
  - stop work (e.g. ‘certified’ workers can halt work they feel is dangerous to other workers)
  - employers must take precautions to protect the health and safety of employees and investigate concerns
  - enforced by Ministry of Labour via inspectors
- Health Protection and Promotion Act (HPPA) (Ontario)
  - Medical Officer of Health has right to investigate and manage health hazards where workplace exposures may impact non-workers (e.g. community members living close to the work site)
- Employment and Social Insurance Act (Each province will have their own similar legislation)
  - Establishes Workplace Safety and Insurance Board (WSIB), an autonomous government agency that oversees workplace safety training and administers insurance for workers and employers
  - WSIB decides benefits for workers, which may include reimbursement for
    - Loss of earned income
    - Non-economic loss (e.g. physical, functional, or psychological loss extending beyond the workplace)
    - Loss of retirement income
    - Health care expenses (e.g. first-aid, medical treatment)
    - Survivor benefits (e.g. dependents and spouses can receive benefits)
  - Employers pay for costs (e.g. no government funding)
  - No-fault insurance (e.g. worker has no right to sue the employer) in return for guaranteed compensation for accepted claims
  - Negligence is not considered a factor
  - Physicians are required to provide the WSIB with information about a worker’s health without a medical waiver once a claim is made

### Workplace Health Promotion and Protection

- take action in the workplace so the worker is protected from injury or illness
  - identifying workplace hazards (e.g. through material safety data sheets [MSDS])
  - assessing risk
  - reducing exposure: changes to work environment including elimination, substitution, and isolation of hazard (e.g. engineering controls) more effective than changes to how people work (e.g. administrative controls) and personal protective equipment

### Workplace Disease Prevention and Identification

- monitor workers’ health to prevent the development of disease
  - periodic examinations to facilitate pre-symptomatic diagnosis
  - PFT for asthma (e.g. occupational dust exposure)
  - audiograms for hearing loss (e.g. occupational noise exposure)
  - substance misuse screening where performance impairment is suspected
- work up and diagnose presenting occupational health problems with appropriate laboratory and radiologic investigations
- Occupational Health Statistics
  - 1 in 68 employed workers in 2010 received workers compensation due to injury or harm on the job
  - 4,405 fatal work injuries in the United States in 2013, rate = 3.2/100,000 workers
  - Source: Employment and Social Development Canada. Work-related injuries, 2015
Workplace Treatment and Rehabilitation

- treat injury or illness with safe return to the workplace
- may require rehabilitation, retraining, change in job duties, and/or workers’ compensation (WSIB)
- advise relevant authorities if necessary (e.g. report notifiable diseases to public health, conditions impeding driving to Ministry of Transportation, see Appendix, PH25)

Appendix – Mandatory Reporting

Reportable Diseases

As an essential part of the health system, physicians in Canada are required by law to report certain diseases to public health for the following reasons

1. to control the outbreak
   - if the disease presents an outbreak threat (e.g. measles, Salmonella, respiratory diseases in institutions)
2. to prevent spread
   - if the disease presents a significant threat to individuals or a subset of the population (e.g. Lassa Fever)
3. for surveillance
   - if the disease is preventable with immunization (e.g. polio, diphtheria, congenital rubella)
4. if infected individuals require education, treatment and/or partner notification (e.g. gonorrhea, TB)
5. reporting details (website, office etc.)
   - some are more urgent than others (must contact MOH)
   - physicians should also report unlisted diseases that appear in clusters

The following list is based on the reportable diseases in Ontario for 2014. Each province will have similar legislation

Source: Health Protection and Promotion Act, O. Reg. 559/91, amended to O. Reg.49/07

Acquired Immunodeficiency Syndrome (AIDS)
Acute flaccid paralysis <15 yr
Amoebiasis
Anthrax
Botulism
Brucellosis
Campylobacter enteritis
Chancroid
Chickenpox (Varicella)
Chlamydia trachomatis infections
Cholera
Clostridium difficile associated disease (CDAD) outbreaks in public hospitals
Cryptosporidiosis
Cyclosporiasis
Cytomegalovirus infection, congenital
diabetes, invasive
Diphtheria
Encephalitis, including:
  i. Primary, viral
  ii. Post-infectious
  iii. Vaccine-related
  iv. Subacute sclerosing panencephalitis
  v. Unspecified
Food poisoning, all causes
Gastroenteritis, institutional outbreaks
Giardiasis, except asymptomatic cases
Gonorrhea
Haemophilus influenzae b disease, invasive
Hantavirus pulmonary syndrome
Hepatitis A
Hepatitis B
Hepatitis C
Hepatitis D (Delta hepatitis)
Herpes, neonatal
Human Immunodeficiency Virus (HIV)
Influenza
Lassa Fever
Legionellosis
Measles
Meningitis, acute:
  i. Bacterial
  ii. Viral
  iii. Other
Meningococcal disease, invasive
Mumps
Paralytic shellfish poisoning
Paratyphoid fever
Pertussis (whooping cough)
Plague
Pneumococcal disease, invasive
Poliomyelitis, acute
Psittacosis/Ornithosis
Q Fever
Rabies
Respiratory infection outbreaks in institutions
Rubella
Rubella, congenital syndrome
Salmonellosis
Severe Acute Respiratory Syndrome (SARS)
Shigellosis
Smallpox
Streptococcal infections, Group A invasive
Streptococcal infections, Group B neonatal
Syphilis
Tetanus
Transmissible spongiform encephalopathy, including:
  i. Creutzfeldt-Jakob disease, all types
  ii. Gerstmann-Sträussler-Scheinker syndrome
  iii. Fatal familial insomnia
  iv. Kuru
Trichinosis
Typhoid Fever
Verotoxin-producing E. coli infection
Yellow Fever
Yersinia pestis
Other Reportable Conditions

In addition to reporting diseases, physicians have a legal responsibility to report certain conditions. The list below highlights some reportable conditions for Ontario, but is not exhaustive. See your jurisdiction’s regulatory body for the full list.

Child Abuse – to local Children’s Aid Society (CAS)
- all child abuse and neglect where reasonable grounds to suspect exist (including physical harm, emotional harm, sexual harm, and neglect)
- duty to report is ongoing: if additional reasonable grounds are suspect, a further report to CAS is necessary

Unfit to Drive – to provincial Ministry of Transportation
- all patients with a medical condition (e.g., dementia, untreated epilepsy) that may impede their driving ability
- if a physician does not report and the driver gets into an accident, the physician may be held liable

Unfit to Fly – to federal Ministry of Transportation
- all patients believed to be flight crew members or air traffic controller with a medical or optometric condition that is likely to constitute a hazard to aviation safety

Gunshots Wounds – to local police service
- all patients with a gunshot or stab wounds
- self-inflicted knife wounds are not reportable


References


Canadian Institute for Health Information. Available from: http://www.cihi.ca.


Health Protection and Promotion Act, R.S.O. 1990, c. H.7; O. Reg. 559/91, amended to O. Reg. 49/07.


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<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT</td>
<td>serotonin</td>
</tr>
<tr>
<td>ACh</td>
<td>acetylcholine</td>
</tr>
<tr>
<td>ACT</td>
<td>assertive community treatment</td>
</tr>
<tr>
<td>ADHD</td>
<td>attention deficit hyperactivity disorder</td>
</tr>
<tr>
<td>AN</td>
<td>anorexia nervosa</td>
</tr>
<tr>
<td>ASD</td>
<td>autism spectrum disorder</td>
</tr>
<tr>
<td>ASPD</td>
<td>antisocial personality disorder</td>
</tr>
<tr>
<td>BN</td>
<td>bulimia nervosa</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behavioural therapy</td>
</tr>
<tr>
<td>CD</td>
<td>conduct disorder</td>
</tr>
<tr>
<td>CRA</td>
<td>community reinforcement approach</td>
</tr>
<tr>
<td>CT</td>
<td>cognitive therapy</td>
</tr>
<tr>
<td>CTO</td>
<td>community treatment order</td>
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<tr>
<td>DA</td>
<td>dopamine</td>
</tr>
<tr>
<td>DZ</td>
<td>dizygotic</td>
</tr>
<tr>
<td>ECT</td>
<td>electroconvulsive therapy</td>
</tr>
<tr>
<td>EPS</td>
<td>extrapyramidal symptoms</td>
</tr>
<tr>
<td>ERB</td>
<td>exposure with response</td>
</tr>
<tr>
<td>EOH</td>
<td>ethanol/ethanol</td>
</tr>
<tr>
<td>GAD</td>
<td>generalized anxiety disorder</td>
</tr>
<tr>
<td>GMC</td>
<td>general medical condition</td>
</tr>
<tr>
<td>IPT</td>
<td>interpersonal therapy</td>
</tr>
<tr>
<td>MAOI</td>
<td>monoamine oxidase inhibitor</td>
</tr>
<tr>
<td>MDD</td>
<td>major depressive disorder</td>
</tr>
<tr>
<td>MDE</td>
<td>major depressive episode</td>
</tr>
<tr>
<td>MSE</td>
<td>motivational enhancement therapy</td>
</tr>
<tr>
<td>MSE</td>
<td>mental status examination</td>
</tr>
<tr>
<td>MST</td>
<td>magnetic stimulation therapy</td>
</tr>
<tr>
<td>NAD</td>
<td>Narcotics Anonymous</td>
</tr>
<tr>
<td>NMS</td>
<td>neuroleptic malignant syndrome</td>
</tr>
<tr>
<td>NO5</td>
<td>not otherwise specified</td>
</tr>
<tr>
<td>OED</td>
<td>obsessive-compulsive disorder</td>
</tr>
<tr>
<td>OCPD</td>
<td>obsessive-compulsive personality disorder</td>
</tr>
<tr>
<td>ODD</td>
<td>oppositional defiant disorder</td>
</tr>
<tr>
<td>PD</td>
<td>personality disorder</td>
</tr>
<tr>
<td>PDD</td>
<td>pervasive developmental disorder</td>
</tr>
<tr>
<td>PTD</td>
<td>post-traumatic stress disorder</td>
</tr>
<tr>
<td>rTMS</td>
<td>repetitive transcranial magnetic stimulation</td>
</tr>
<tr>
<td>SSRI</td>
<td>serotonin and norepinephrine reuptake inhibitors</td>
</tr>
<tr>
<td>SSRI</td>
<td>selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TCA</td>
<td>tricyclic antidepressant</td>
</tr>
</tbody>
</table>

## Psychiatric Assessment

### History

**Identifying Data**
- necessary: name, sex, age, ethnicity, marital status, occupation/source of financial support, place and type of residency
- adjunct: makeup of household, religion, education, referral source, known or unknown to treatment team

**Reliability of Patient as a Historian**
- Indicate if, and for what content, collateral source used (e.g. parent, teacher) if patient unable/unwilling to cooperate

**Chief Complaint**
- in patient’s own words, duration

**History of Present Illness**
- reason for seeking help (that day), current symptoms (onset, duration and course), stressors, supports, functional status, relevant associated symptoms (pertinent positives and negatives)
- safety screen: is the patient endangering self or others? dependants at home (e.g. children, pets), ability to drive safely, ability to care for self (e.g. eating, hygiene, taking medications)

### Psychiatric Functional Inquiry

- mood: depression, mania
- anxiety: worries, obsessions, compulsions, panic attacks, phobias, history of trauma
- psychosis: hallucinations, delusions
- suicide/homicide: ideation, plan, intent, history of attempts (see Suicide, PS4)
- organic: EtOH/drug use or withdrawal, illness, dementia

### Past Psychiatric History
- all previous psychiatric diagnoses, psychiatric contacts, treatments (pharmacological and non-pharmacological), and hospitalizations
- include past suicide attempts, substance use/abuse, and legal problems

### Past Medical/Surgical History
- all medical, surgical, neurological (e.g. head trauma, seizures), and psychosomatic illnesses
- current medications, allergies

### Family Psychiatric/Medical History
- family members: ages, occupations, personalities, medical or genetic illnesses and treatments, relationships with parents/siblings
- family psychiatric history: any past or current psychiatric illnesses and hospitalizations, suicide, substance abuse

### Past Personal/Developmental History (as relevant)
- prenatal and perinatal history (desired vs. unwanted pregnancy, maternal and fetal health, domestic violence, maternal substance use, complications of pregnancy/delivery)
- early childhood to age 3 (developmental milestones, activity/attention level, family stability, attachment figures)
- middle childhood to age 11 (school performance, peer relationships, fire-setting, stealing, incontinence)
- late childhood to adolescence (drug/alcohol, legal problems, peer and family relationships)
- physical or sexual abuse in childhood/adolescence
- adulthood (education, occupations, relationships)
- personality before current illness, recent changes in personality
- psychosocial history (puberty, first sexual encounter, romantic relationships, gender roles, sexual dysfunction)

### Screening Questions for Major Psychiatric Disorders

- Have you been feeling down, depressed or hopeless?
- Do you feel anxious or worry about things?
- Has there been a time in your life where you have felt euphoric, extremely talkative, had a lot of energy, and a decreased need for sleep?
- Do you see or hear things that you think other people cannot?
- Have you ever thought of harming yourself or committing suicide?
Mental Status Exam

General Appearance
• dress, grooming, posture, gait, physical characteristics, body habitus, apparent vs. chronological age, facial expression (e.g. sad, suspicious), tattoos, piercings (if numerous or atypical), acute distress or relaxed

Behaviour
• psychomotor activity (agitation, retardation), abnormal movements or lack thereof (tremors, akathisia, tardive dyskinesia, paralysis), attention level and eye contact, attitude toward examiner (ability to interact, level of cooperation)

Speech
• rate (e.g. pressured, slowed), rhythm/fluency, volume, tone, articulation, quantity, spontaneity

Mood and Affect
• mood: subjective emotional state (in patient's own words)
• affect: objective emotional state inferred from emotional responses to stimuli; described in terms of
  ▪ quality (euthymic, depressed, elevated, anxious, irritable)
  ▪ range (full, restricted, flat, blunted)
  ▪ stability (fixed, labile)
  ▪ mood congruence (inferred by reader by comparing mood and affect descriptions)
  ▪ appropriateness to thought content
• some clinicians use 0-10 scales when rating mood to help get a subjective norm for each patient that can help establish changes over time and with treatment

Thought Process/Form
• coherence (coherent, incoherent)
• logic (logical, illogical)
• stream
  ▪ goal-directed: clearly answers questions in a linear, organized, logical fashion
  ▪ circumstantial: speech that is indirect and delayed in reaching its goal; eventually comes back to the point
  ▪ tangential: speech is oblique or irrelevant; does not come back to the original point
  ▪ loosening of associations/ derailment: illogical shifting between topics
  ▪ flight of ideas: quickly skipping from one idea to another where the ideas are marginally connected, usually associated withmania
  ▪ word salad: jumble of words lacking meaning or logical coherence
  ▪ perseveration: repetition of the same verbal or motor response to stimuli
  ▪ echolalia: repetition of phrases or words spoken by someone else
  ▪ thought blocking: sudden cessation of flow of thought and speech
  ▪ clang associations: speech based on sound such as rhyming or punning
  ▪ neologism: use of novel words or of existing words in a novel fashion

Thought Content
• suicidal ideation/homicidal ideation
  ▪ frequency and pervasiveness of thoughts, formulation of plan, means to plan, intent, active vs. passive, protective factors
• preoccupations, ruminations: reflections/thoughts at length, not fixed or false
• obsession: recurrent and persistent thought, impulse, or image which is intrusive or inappropriate and unwanted
  ▪ cannot be stopped by logic or reason
  ▪ causes marked anxiety and distress
  ▪ common themes: contamination, orderliness, sexual, pathological doubt/worry/guilt
  ▪ magical thinking: belief that thinking something will make it happen; normal in children and certain cultures
• ideas of reference: similar to delusion of reference, but less fixed (the reality of the belief is questioned)
• overvalued ideas: unusual/odd beliefs that are not of delusional proportions
• first rank symptoms of schizophrenia: thought insertion/withdrawal/broadcasting
• delusion: a fixed false belief that is out of keeping with a person’s cultural or religious background and is firmly held despite incontrovertible proof to the contrary

Perception
• hallucination: sensory perception in the absence of external stimuli that is similar in quality to a true perception
  ▪ auditory (most common), visual, gustatory, olfactory, tactile
  ▪ illusion: misperception of a real external stimulus (such as mistaking a coat on a rack as a person late at night)
• depersonalization: change in self-awareness such that the person feels unreal, distant, or detached from his or her body, and/or unable to feel emotion
• derealization: feeling that the world/outer environment is unreal
Cognition
- level of consciousness (alert, reduced, obtunded)
- orientation: time, place, person
- memory: immediate, recent, remote
- global evaluation of intellect (below average, average, above average, in keeping with person's education)
- intellectual functions: attention, concentration, calculation, abstraction (proverb interpretation, similarities test), language, communication
- MMSE/MOCA useful as standardized assessment of cognition

Insight
- patient's ability to realize that he or she has a physical or mental illness and to understand its implications (no, limited, partial, full)

Judgment
- patient's ability to understand relationships between facts and draw conclusions that determine one's actions

Assessment and Plan

Historical Multiaxial Model
- since DSM-5, this Model is no longer used for psychiatric diagnosis. Instead, relevant psychiatric and medical diagnoses are simply listed. Nevertheless, we offer it here as a possible framework for psychiatric patient assessment, as many physicians still employ it.

Multiaxial Assessment
- Axis I: differential diagnosis of DSM-5 clinical disorders
- Axis II: personality disorders, developmental disability
- Axis III: general medical conditions potentially relevant to understanding/management of the mental disorder
- Axis IV: psychosocial and environmental issues
- Axis V: Global Assessment of Functioning (GAF, 0 to 100) incorporating effects of axes I to IV

After History and MSE, the assessment and plan is recorded

Assessment/Problem Formulation
- identify predominant symptom cluster (mood, anxiety, psychosis, organic) - causing the most distress/interference, persist when other symptom categories not present (e.g. psychosis in the absence of mood symptoms)
- dominating symptoms will direct differential
c- consider current issues as they relate to an individual's factors in three domains: biological, psychological, and social
d- for each category: predisposing, precipitating, perpetuating, and protecting factors are considered

Approach to Management
- consider short-term and long-term, and three types: biological (e.g. pharmacotherapy), psychological (e.g. CBT), and social (e.g. support group)

Suicide

Importance
- absolutely must be screened for in every encounter; part of risk assessment along with violent/homicidal ideation

Approach
- ask every patient – e.g. “Have you had any thoughts of wanting to kill yourself?”
- classify ideation
  - passive ideation: would rather not be alive but has no active plan for suicide
    - e.g. “I’d rather not wake up” or “I would not mind if a car hit me”
  - active ideation
    - e.g. “I think about killing myself”
- assess risk
  - plan: “Do you have a plan as to how you would end your life?”
  - intent: “Do you think you would actually carry out this plan?” “If not, why not?”
  - past attempts: highest risk if previous attempt in past year
  - ask about lethality, outcome, medical intervention
- assess suicidal ideation
  - onset and frequency of thoughts: “When did this start?” or “How often do you have these thoughts?”
• control over suicidal ideation: "How do you cope when you have these thoughts?" “Could you call someone for help?”
• intended lethality: “Do you want to end your life?” or “What do you think would happen if you actually took those pills?”
• access to means: “How will you get a gun?” or “Which bridge do you think you would go to?”
• time and place: “Have you picked a date and place? Is it in an isolated location?”
• provocative factors: “What makes you feel worse (e.g. being alone)?”
• protective factors: “What keeps you alive (e.g. friends, family, pets, faith, therapist)?”
• final arrangements: “Have you written a suicide note? Made a will? Given away your belongings?”
• practiced suicide or aborted attempts: “Have you ever put the gun to your head?” “Held the medications in your hand?” “Stood at the bridge?”
• ambivalence: “I wonder if there is a part of you that wants to live, given that you came here for help?”

Assessment of Suicide Attempt
• setting (isolated vs. others present/chance of discovery)
• planned vs. impulsive attempt, triggers/stressors
• substance use/intoxication
• medical attention (brought in by another person vs. brought in by self to ED)
• time lag from suicide attempt to ED arrival
• expectation of lethality, dying
• reaction to survival (guilt/remorse vs. disappointment/self-blame)

Epidemiology
• attempted:completed = 20:1
• M:F = 1:4 for attempts, 3:1 for completed

Risk Factors
• epidemiologic factors
  • age: increases after age 14, second most common cause of death for ages 15-24, highest rates in persons >65 yr
  • sex: male
  • race/ethnic background: white or Native Canadians on reserves
  • marital status: widowed/divorced
  • living situation: alone; no children <18 yr old in the household
  • other: stressful life events, access to firearms
• psychiatric disorders
  • mood disorders (15% lifetime risk in depression; higher in bipolar)
  • anxiety disorders (especially panic disorder)
  • schizophrenia (10-15% risk)
  • substance abuse (especially alcohol – 15% lifetime risk)
  • eating disorders (5% lifetime risk)
  • adjustment disorder
  • conduct disorder
  • personality disorders (borderline, antisocial)
• past history
  • prior suicide attempt
  • family history of suicide attempt/completion

Clinical Presentation
• symptoms associated with suicide
  • hopelessness
  • anhedonia
  • insomnia
  • severe anxiety
  • impaired concentration
  • psychomotor agitation
  • panic attacks

Management
• proper documentation of the clinical encounter and rationale for management is essential
  • higher risk (hospitalization needs to be strongly considered):
    • patients with a plan and intention to act on the plan, access to lethal means, recent social stressors, and symptoms suggestive of a psychiatric disorder
    • do not leave patient alone; remove potentially dangerous objects from room
    • if patient refuses to be hospitalized, complete form for involuntary admission (Form 1)
  • lower risk
    • patients who are not actively suicidal, with no plan or access to lethal means

Suicide Risk Factors
SAD PERSONS
Sex (male)
Age >60 yr old
Depression
Previous attempts
Ethanol abuse
Rational thinking loss (delusions, hallucinations, hopelessness)
Suicide in family
Organized plan
No spouse (no support systems)
Serious illness, intractable pain

Suicidal Ideation Assessment
• Asking patients about suicide will not give them the idea or the incentive to commit suicide
• The best predictor of completed suicide is a history of attempted suicide
• The most common psychiatric disorders associated with completed suicide are mood disorders and alcohol abuse
• discuss protective factors and supports in their life, remind them of what they live for, 
  promote survival skills that helped them through previous suicide attempts 
• make a safety plan that could include an agreement that they will: 
  • not harm themselves 
  • avoid alcohol, drugs, and situations that may trigger suicidal thoughts 
  • follow-up with you at a designated time 
  • contact a health care worker, call a crisis line, or go to an emergency department if they 
    feel unsafe or if their suicidal feelings return or intensify 
• depression: consider hospitalization if symptoms severe or if psychotic features are present; 
  otherwise outpatient treatment with good supports and SSRIs/SNRIs 
• alcohol-related: usually resolves with abstinence for a few days; if not, suspect depression 
• personality disorders: crisis intervention, may or may not hospitalize 
• schizophrenia/psychosis: hospitalization might be necessary 
• parasuicide/self-mutilation: long-term psychotherapy with brief crisis intervention when necessary 

**Psychotic Disorders**

**Definition**
- characterized by a significant impairment in reality testing
- delusions or hallucinations (with/without insight into their pathological nature) behaving in a 
  disorganized way so that it is reasonable to infer that reality testing is disturbed

**Differential Diagnosis of Psychosis**

**Approach**
- to differentiate among psychotic disorders and distinguish them from other primary diagnoses 
  with psychotic features, 
- consider symptoms, persistence, and time 
- symptoms: what symptoms exist? The primary diagnosis needs full criteria to be met 
  • mood: depressive episodes with psychotic features, manic episodes with psychotic features 
  • psychotic: consider symptoms in Criterion A of schizophrenia, such as delusions, 
    hallucinations, disorganized speech, grossly disorganized/catatonic behaviour, negative 
    symptoms (i.e. diminished emotional expression or avolition) 
- persistence: is there a time when certain symptom clusters are present without other clusters? 
  • e.g. if there is a period of time with mood symptoms but not psychotic symptoms, consider 
    mood disorder 
  • e.g. if two weeks where psychotic symptoms persist in the absence of mood symptoms, 
    consider schizoaffective disorder 
- time: how long have the symptoms been present?

**Differential**
- primary psychotic disorders: schizophrenia, schizophreniform, brief psychotic, schizoaffective, 
  delusional disorder 
- mood disorders: depression with psychotic features, bipolar disorder (manic or depressive episode 
  with psychotic features) 
- personality disorders: schizotypal, schizoid, borderline, paranoid, obsessive-compulsive 
- general medical conditions: tumour, head trauma, dementia, delirium, metabolic, infection, stroke, 
  temporal lobe epilepsy 
- substance-induced psychosis: intoxication or withdrawal, prescribed medications, toxins

**Table 1. Differentiating Psychotic Disorders**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Psychotic Symptoms</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief Psychotic Disorder</td>
<td>≥1 positive symptoms of criterion A</td>
<td>&lt;1 mo</td>
</tr>
<tr>
<td>Schizophreniform Disorder</td>
<td>Criterion A</td>
<td>1-6 mo</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Criterion A</td>
<td>&gt; 6 mo</td>
</tr>
<tr>
<td>Schizoaffective Disorder</td>
<td>Criterion A + major mood episode, but ≥2 wk psychotic without mood symptoms</td>
<td>&gt; 1 mo</td>
</tr>
<tr>
<td>Delusional Disorder</td>
<td>Non-bizarre delusions, hallucinations</td>
<td>&gt; 1 mo</td>
</tr>
<tr>
<td>2º to Substance Intoxication/Withdrawal</td>
<td>Delusions or hallucinations During intoxication/withdrawal, not &gt; 1 mo without use</td>
<td></td>
</tr>
<tr>
<td>2º to Mood Disorder</td>
<td>Mood symptoms dominant + delusions/hallucinations (mood congruent)</td>
<td>Psychosis may be present for the duration of the mood episode</td>
</tr>
</tbody>
</table>

**Management of Acute Psychosis and Mania**
- Ensure safety of self, patient, and other patients 
- Have an exit strategy 
- Decrease stimulation 
- Assume a non-threatening stance 
- IM medications (benzodiazepine + antipsychotic) often needed as patient may refuse oral medication 
- Physical restraints may be necessary 
- Do not use antidepressants or stimulants
**Schizophrenia**

**DSM-5 Diagnostic Criteria for Schizophrenia**
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. two (or more) of the following, each present for a significant portion of time during a 1 mo period (or less if successfully treated). At least one of these must be (1), (2), or (3)
1. delusions
2. hallucinations
3. disorganized speech (e.g. frequent derailment or incoherence)
4. grossly disorganized or catatonic behaviour
5. negative symptoms (i.e. diminished emotional expression or avolition)

B. decreased level of function: for a significant portion of time since onset, one or more major areas affected (e.g. work, interpersonal relations, self-care) is markedly decreased (or if childhood/adult onset, failure to achieve expected level)

C. at least 6 mo of continuous signs of the disturbance. Must include at least 1 mo of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms) and may include periods of prodromal or residual symptoms (during which, disturbance may manifest by only negative symptoms or by two or more Criterion A symptoms present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences)

D. rule out schizoaffective disorder and depressive or bipolar disorder with psychotic features because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness

E. rule out other causes: GMC, substances (e.g. drug of abuse, medication)

F. if history of autism spectrum disorder or communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least 1 mo (or less if successfully treated)

• **specifiers:** type of episode (e.g. first episode, multiple episodes, continuous), with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis (in acute episode, in partial remission, in full remission)

**Epidemiology**
- prevalence: 0.3-0.7%, M:F = 1:1
- mean age of onset: females late-20s; males early- to mid-20s
- suicide risk: 10% die by suicide, 30% attempt suicide

**Etiology**
- multifactorial: disorder is a result of interaction between both biological and environmental factors
  - genetic: 40% concordance in monozygotic (MZ) twins; 46% if both parents have schizophrenia; 10% of dizygotic (DZ) twins, siblings, children affected; vulnerable genes include Disrupted-in-Schizophrenia 1 (DISC1); neuregulin 1 (NRG 1); dystrobrevin binding protein / dysbindin (DTNBP1); catechol-O-methyltransferase (COMT); danino acid oxidase activator (DAOA); metabotropic glutamate receptor 3 (GRM3); and brain-derived neurotrophic factor (BDNF)
  - neurochemistry (“dopamine hypothesis”): excess activity in the mesolimbic dopamine pathway may mediate the positive symptoms of psychosis, while decreased dopamine in the prefrontal cortex may mediate negative and cognitive symptoms. GABA, glutamate, and ACh dysfunction are also thought to be involved
  - neuroanatomy: decreased frontal lobe function; asymmetric temporal/limbic function; decreased basal ganglia function; subtle changes in thalamus, cortex, corpus callosum, and ventricles; cytoarchitectural abnormalities
  - neuroendocrinology: abnormal growth hormone, prolactin, cortisol, and ACTH
  - neuropsychology: global defects seen in attention, language, and memory suggest lack of connectivity of neural networks
  - environmental: indirect evidence of cannabis use, geographical variance, winter season of birth, obstetrical complications, and prenatal viral exposure

**Pathophysiology**
- neurodegenerative theory
- natural history may be a rapid or gradual decline in function and ability to communicate
- glutamate system may mediate progressive degeneration by excitotoxic mechanism which leads to production of free radicals
- neurodevelopmental theory: abnormal development of the brain from prenatal life
- neurons fail to migrate correctly, make inappropriate connections, and break down in later life
- inappropriate apoptosis during neurodevelopment resulting in faulty connections between neurons

**Comorbidity**
- substance-related disorders
- anxiety disorders
- decreased life expectancy because of associated medical conditions (e.g. weight gain, diabetes, metabolic syndrome, CV/pulmonary disease)

**Disorganized Behaviours in Schizophrenia**
- Catatonic stupor: fully conscious, but immobile, mute, and unresponsive
- Catatonic excitement: uncontrolled and aimless motor activity, maintaining bizarre positions for a long time
- Stereotypy: repeated but non-goal-directed movement (e.g. rocking)
- Maniamerisms: goal-directed activities that are odd or out of context (e.g. grimacing)
- Echopraxia: imitates movements and gestures of another
- Automatic obedience: carries out simple commands in robot-like fashion
- Negativism: refuses to cooperate with simple requests for no apparent reason
- Inappropriate affect, neglect of self-care, other odd behaviours (random shouting)

**Relationship Between Duration of Untreated Psychosis (DUP) and Outcome in First-Episode Schizophrenia**
- **Purpose:** To review the association between DUP and symptom severity at first treatment contact, and between DUP and treatment outcomes.
- **Study Characteristics:** Critical review and meta-analysis of 43 studies with 4,177 patients.
- **Participants:** Patients with non-affective psychotic disorders at or close to first treatment.
- **Results:** Shorter DUP was associated with greater response to antipsychotic treatment, as measured by global psychopathology, positive symptoms, negative symptoms, and functional outcomes. At the time of treatment initiation, longer DUP was associated with the severity of negative symptoms but not with the severity of positive symptoms, global psychopathology, or neurocognitive function.
- **Conclusions:** DUP may be a potentially modifiable prognostic factor.
Management of Schizophrenia
- biological / somatic
  - acute treatment and maintenance: antipsychotics (haloperidol, risperidone, olanzapine, paliperidone, clozapine if refractory); often regimens of IM q2-4 weeks used in severe cases to ensure compliance
  - adjunctive: ± mood stabilizers (for aggression/impulsiveness - lithium, valproate, carbamazepine) ± anxiolytics ± ECT
  - treat for at least 1-2 years after the first episode, at least 5 years after multiple episodes (relapse causes severe deterioration)
- psychosocial
- psychotherapy: individual, family (important), group: supportive, CBT (see Table 14, PS43)
  - ACT (Assertive Community Treatment): mobile mental health teams that provide individualized treatment in the community and help patients with medication adherence, basic living skills, social support, job placements, resources
- social skills training, employment programs, disability benefits
- housing (group home, boarding home, transitional home)

Course and Prognosis
- majority of individuals display some type of prodromal phase
- course is variable: some individuals have exacerbations and remissions and others remain chronically ill; accurate prediction of the long-term outcome is not possible
- negative symptoms may be prominent early in the illness and may become more prominent and more disabling later on; positive symptoms appear and typically diminish with treatment
- over time: 1/3 improve, 1/3 remain the same, 1/3 worsen

Schizophreniform Disorder
Diagnosis
- criteria A, D, and E of schizophrenia are met; but episode lasts for at least 1 mo but less than 6 mo
- if the symptoms have extended past 6 mo the diagnosis becomes schizophrenia
- specifiers: with/without good prognostic features (e.g. acute onset, confusion, good premorbid functioning, absence of blunt/flat affect), with catatonia, current severity based on quantitative assessment of primary symptoms of psychosis

Treatment
- similar to acute schizophrenia

Prognosis
- better than schizophrenia; begins and ends more abruptly; good pre- and post-morbid function

Brief Psychotic Disorder
Diagnosis
- criteria A1-A4, D, and E of schizophrenia are met; an episode of the disorder lasts for at least 1 d, but less than 1 mo with eventual full return to premorbid level of functioning
- specifiers: with/without marked stressors, with postpartum onset, with catatonia, current severity
- can occur after a stressful event or postpartum (see Postpartum Mood Disorders, PS12)

Treatment
- secure environment, antipsychotics, anxiolytics

Prognosis
- good, self-limiting, should return to pre-morbid function within 1 mo

Schizoaffective Disorder
DSM-5 Diagnostic Criteria for Schizoaffective Disorder (Reformatted)
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A. concurrent psychosis (criterion A of schizophrenia) and major mood episode - uninterrupted period of illness
B. delusions or hallucinations for 2 or more wk in the absence of a major mood episode during the lifetime duration of the illness
C. major mood episode symptoms are present for the majority of the total duration of the active and residual periods of the illness
D. the disturbance is not attributable to the effects of a substance or another medical condition
- specifiers: bipolar type, depressive type, with catatonia, type of episode, severity
- one-third as prevalent as schizophrenia; schizoaffective disorder bipolar type more common in young adults, schizoaffective disorder depressive type more common in older adults
- depressive symptoms correlated with higher suicide risk
Treatment
• antipsychotics, mood stabilizers, antidepressants

Prognosis
• between that of schizophrenia and of mood disorder

Delusional Disorder

DSM-5 Diagnostic Criteria for Delusional Disorder
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A. the presence of one (or more) delusions with a duration of 1 mo or longer
B. criterion A for schizophrenia has never been met
    Note: hallucinations, if present, are not prominent and are related to the delusional theme
C. apart from the impact of the delusion(s) or its ramifications, functioning is not markedly impaired, and behaviour is not obviously bizarre or odd
D. if manic or major depressive episodes have occurred, these have been brief relative to the duration of the delusional periods
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition and is not better explained by another mental disorder
• subtypes: erotomanic, grandiose, jealous, persecutory, somatic, mixed, unspecified
• further specify: bizarre content, type of episode (e.g. first episode, multiple episode), severity

Treatment
• psychotherapy, antipsychotics, antidepressants

Prognosis
• chronic, unremitting course but high level of functioning; a portion will progress to schizophrenia

Mood Disorders

Definitions
• mood disorders are characterized by the presence of diagnosable mood episodes
• mood episodes represent a combination of symptoms comprising a predominant mood state that is abnormal in quality or duration (e.g. major depressive, manic, mixed, hypomanic). DSM-5 Criteria for mood episodes are listed below.
• types of mood disorders include
• depressive (major depressive disorder, persistent depressive disorder)
• bipolar (bipolar I/II disorder, cyclothymia)
• secondary to general medical condition, substances, medications, other psychiatric issue
• accurate diagnosis of a mood disorder requires a careful past medical and psychiatric history to detect past mood episodes and to rule out whether these episodes were secondary to substance use, a medical condition, a loss, etc.

Medical Workup of Mood Disorder
• routine screening: physical exam, CBC, thyroid function test, extended electrolytes, urinalysis, drug screen, medications list
• additional screening: neurological consultation, chest X-ray, ECG, CT head

Mood Episodes

DSM-5 Diagnostic Criteria for Major Depressive Episode
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A. ≥5 of the following symptoms have been present during the same 2 wk period and represent a change from previous functioning; at least one of the symptoms is either 1) depressed mood or 2) loss of interest or pleasure (anhedonia)
    Note: Do not include symptoms that are clearly attributable to another medical condition
• depressed mood most of the day, nearly every day, as indicated by either subjective report or observation made by others
• markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day
• significant and unintentional weight loss, weight gain, or decrease/increase in appetite nearly every day
• insomnia or hypersomnia nearly every day
• psychomotor agitation or retardation nearly every day
• fatigue or loss of energy nearly every day
• feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick)
- diminished ability to think or concentrate, or indecisiveness, nearly every day
- recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide
B. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
C. the episode is not attributable to the direct physiological effects of a substance or a GMC

**DSM-5 Criteria for Manic Episode**
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A. a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting $\geq 1$ wk and present most of the day, nearly every day (or any duration if hospitalization is necessary)
B. during the period of mood disturbance and increased energy or activity, $\geq 3$ of the following symptoms have persisted (4 if the mood is only irritable) and have been present to a significant degree and represent a noticeable change from usual behaviour
  - inflated self-esteem or grandiosity
  - decreased need for sleep (e.g. feels rested after only 3 h of sleep)
  - more talkative than usual or pressure to keep talking
  - flight of ideas or subjective experience that thoughts are racing
  - distractibility (i.e. attention too easily drawn to unimportant or irrelevant external stimuli)
  - increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
  - excessive involvement in pleasurable activities that have a high potential for painful consequences (e.g. engaging in unrestrained shopping sprees, sexual indiscretions, or foolish business investments)
C. the mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features
D. the episode is not attributable to the physiological effects of a substance or another medical condition

**Hypomanic Episode**
- criterion A and B of a manic episode is met, but duration is $\geq 4$ d
- episode associated with an uncharacteristic change in functioning that is observable by others but not severe enough to cause marked impairment in social or occupational functioning or to necessitate hospitalization
- absence of psychotic features. (If these are present the episode is, by definition, manic)

**Mixed Features**
- an episode specifier in bipolar or depression that indicates the presence of both depressive and manic symptoms concurrently, classified by the disorder and primary mood episode component (e.g. bipolar disorder, current episode manic, with mixed features)
- clinical importance due to increased suicide risk
- if found in patient diagnosed with major depression, high index of suspicion for bipolar disorder
- while meeting the full criteria for a major depressive episode, the patient has on most days $\geq 3$ of criteria B for a manic episode
- while meeting the full criteria for a manic/hypomanic episode, the patient has on most days $\geq 3$ of criteria A for a depressive episode. (The following criterion A cannot count: psychomotor agitation, insomnia, difficulties concentrating, weight changes)

**Depressive Disorders**

**MAJOR DEPRESSIVE DISORDER**

**DSM-5 Diagnostic Criteria for Major Depressive Disorder (MDD)**
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A. presence of a MDE
B. the MDE is not better accounted for by schizoaffective disorder and is not superimposed on schizophrenia, schizophreniform disorder, delusional disorder, or psychotic disorder NOS
C. there has never been a manic episode or a hypomanic episode

**Note:** This exclusion does not apply if all of the manic-like, or hypomanic-like episodes are substance or treatment-induced or are due to the direct physiological effects of another medical condition

**specifiers:** with anxious distress, mixed features, melancholic features, atypical features, mood-congruent psychotic features, mood-incongruent psychotic features, catatonia, peripartum onset, seasonal pattern
single vs. recurrent is an episode descriptor that carries prognostic significance. Recurrent is classified as the patient having two or more distinct MDE episodes; to be considered separate the patient must have gone 2 consecutive months without meeting criteria.

**Epidemiology**
- lifetime prevalence: 12%
- peak prevalence age 15-25 yr (M:F = 1:2)

**Etiology**
- biological
  - genetic: 65-75% MZ twins; 14-19% DZ twins, 2-4 fold increased risk in first-degree relatives
  - neurotransmitter dysfunction: decreased activity of 5-HT, NE, and DA at the level of the synapse; changes in GABA and glutamate; various changes in brain circuitry and functional connectivity detectable by fMRI
  - neuroendocrine dysfunction: excessive HPA axis activity
  - neuroanatomy: decreased hippocampal volume, increased ventricle sizes
  - neurophysiologic: decreased REM latency and slow-wave sleep; increased REM length
  - immunologic: increased pro-inflammatory cytokines IL-6 and TNF
  - secondary to medical condition, medication, substance use disorder
- psychosocial
  - psychodynamic (e.g. low self-esteem, unconscious aggression towards self or loved ones, disordered attachment)
  - cognitive (e.g. distorted schemata, Beck’s cognitive triad: negative views of the self, the world, and the future)
  - environmental factors (e.g. job loss, bereavement, history of abuse or neglect, early life adversity)
  - comorbid psychiatric diagnoses (e.g. anxiety, substance abuse, developmental disability, dementia, eating disorder)

**Risk Factors**
- sex: F>M, 2:1
- family history: depression, alcohol abuse, suicide attempt or completion
- childhood experiences: loss of parent before age 11, negative home environment (abuse, neglect)
- personality: neuroticism, insecure, dependent, obsessive
- recent stressors: illness, financial, legal, relational, academic
- lack of intimate, confiding relationships or social isolation
- low socioeconomic status

**Depression in the Elderly**
- affects about 15% of community residents >65 yr old; up to 50% in nursing homes
- high suicide risk due to social isolation, chronic medical illness, decreased independence
- suicide peak: males aged 80-90; females aged 50-65
- dysthymia may not be a reliable indicator of depression in those >85 yr
- often present with somatic complaints (e.g. changes in weight, sleep, energy) or anxiety symptoms
- may have prominent cognitive changes after onset of mood symptoms (dementia syndrome of depression)
- see Table 3, PS22, for a comparison of delirium and dementia

**Treatment**
- lifestyle: increased aerobic exercise, mindfulness-based stress reduction, zinc supplementation
- biological: SSRIs, SNRIs, other antidepressants, somatic therapies (see Pharmacotherapy, PS44, and Somatic Therapies, PS52)
- 1st line pharmacotherapy: sertraline, escitalopram, venlafaxine, mirtazapine
- for partial or non-response can change class or add augmenting agent: bupropion, quetiapine-XR, aripiprazole, lithium
- typical response to antidepressant treatment: physical symptoms improve at 2 wk, mood/cognition by 4 wk, if no improvement after 4 wk at a therapeutic dosage alter regimen
- ECT: currently fastest and most effective treatment for MDD. Consider in severe, psychotic or treatment-resistant cases
- rTMS: early data support efficacy equivalent to ECT with good safety and tolerability
- phototherapy: especially if seasonal component, shift work, sleep dysregulation
- psychological
  - individual therapy (psychodynamic, interpersonal, CBT), family therapy, group therapy
  - social: vocational rehabilitation, social skills training
  - experimental: magnetic seizure therapy, deep brain stimulation, vagal nerve stimulation, ketamine

**Prognosis**
- one year after diagnosis of MDD without treatment: 40% of individuals still have symptoms that are sufficiently severe to meet criteria for MDD, 20% continue to have some symptoms that no longer meet criteria for MDD, 40% have no mood disorder
PERSISTENT DEPRESSIVE DISORDER

DSM-5 Diagnostic Criteria for Persistent Depressive Disorder

Note: in DSM-IV-TR this was referred to as Dysthymia

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A. depressed mood for most of the day, for more days than not, as indicated either by subjective account or observation by others, for ≥2 yr
B. presence, while depressed, of ≥2 of the following
   • poor appetite or overeating
   • insomnia or hypersomnia
   • low energy or fatigue
   • low self-esteem
   • poor concentration or difficulty making decisions
   • feelings of hopelessness
C. during the 2 yr period (1 yr for children or adolescents) of the disturbance, the person has never been without the symptoms in criteria A and B for more than 2 mo at a time
D. criteria for a major depressive disorder may be continuously present for 2 yr
E. there has never been a manic episode or a hypomanic episode, and criteria have never been met for cyclothymic disorder
F. the disturbance is not better explained by a persistent schizoaffective disorder, schizophrenia, delusional disorder, or other specified or unspecified schizophrenia spectrum and other psychotic disorder.
G. the symptoms are not due to the direct physiological effects of a substance or another medical condition
H. the symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

Epidemiology

• lifetime prevalence: 2-3%; M=F

Treatment

• psychological
  • traditionally psychotherapy was the principal treatment for dysthymia; recent evidence suggests some benefit but generally inferior to pharmacological treatment. Combinations of the two may be most efficacious
  • biological
    • antidepressant therapy: SSRIs (e.g. sertraline, paroxetine) TCAs (e.g. imipramine) as an outpatient

Postpartum Mood Disorders

Postpartum “Blues”

• transient period of mild depression, mood instability, anxiety, decreased concentration; considered to be normal changes in response to fluctuating hormonal levels, the stress of childbirth, and the increased responsibilities of motherhood
• occurs in 50-80% of mothers; begins 2-4 d postpartum, usually lasts 48 h, can last up to 10 d
• does not require psychotropic medication
• usually mild or absent: feelings of inadequacy, anhedonia, thoughts of harming baby, suicidal thoughts

MAJOR DEPRESSIVE DISORDER WITH PERIPARTUM ONSET
(PARTUM DEPRESSION)

Diagnosis

• MDD that occurs during pregnancy or in the 4 wk following delivery

Clinical Presentation

• typically lasts 2-6 mo; residual symptoms can last up to 1 yr
• may present with psychosis; rare (0.2%), usually associated with mania, but also with MDE
• severe symptoms include extreme disinterest in baby, suicidal and infanticidal ideation

Epidemiology

• occurs in 10% of mothers, risk of recurrence 50%

Risk Factors

• previous history of a mood disorder (postpartum or otherwise), family history of mood disorder
• psychosocial factors: stressful life events, unemployment, marital conflict, lack of social support, unwanted pregnancy, colicky or sick infant

Selective Serotonin Reuptake Inhibitors in Pregnancy and Infant Outcomes

Pediatr Child Health 2011;16:562-563

Study: Canadian Paediatric Society (CPS) Clinical practice guidelines.

Recommendations: It is important to treat depression in pregnancy. There is no evidence that SSRIs increase the risk of major malformations. There is conflicting evidence concerning the association of paroxetine and cardiac malformations. SSRIs are not contraindicated while breast-feeding.
Treatment
• psychotherapy (CBT or IPT)
• short-term safety of maternal SSRIs for breastfeeding infants established; long-term effects unknown
• if depression severe or psychotic symptoms present, consider ECT

Prognosis
• impact on child development: increased risk of cognitive delay, insecure attachment, behavioural disorders
• treatment of mother improves outcome for child at 8 mo through increased mother-child interaction

Bipolar Disorders

BIPOLAR I / BIPOLAR II DISORDER

Definition
• Bipolar I Disorder
  • disorder in which at least one manic episode has occurred
  • if manic symptoms lead to hospitalization, or if there are psychotic symptoms, the diagnosis is BP I
  • commonly accompanied by at least 1 MDE but not required for diagnosis
  • time spent in mood episodes: 53% asymptomatic, 32% depressed, 9% cycling/mixed, 6% hypo/manic
• Bipolar II Disorder
  • disorder in which there is at least 1 MDE, 1 hypomanic and no manic episodes
  • while hypomania is less severe than mania, Bipolar II is not a “milder” form of Bipolar I
  • time spent in mood episodes: 46% asymptomatic, 50% depressed, 1% cycling/mixed, 2% hypo/manic
  • a great masquerader, Bipolar II is often missed due to the severity and chronicity of depressive episodes and low rates of spontaneous reporting and recognition of hypomanic episodes

Classification
• classification of bipolar disorder involves describing the disorder (I or II) and the current or most recent mood episode as either manic, hypomorphic, or depressed
• specifiers: with anxious distress, depressed with mixed features, hypo/manic with mixed features, melancholic features, atypical features, mood-congruent or -incongruent psychotic features, catatonia, peripartum onset, seasonal pattern, rapid cycling (4+ mood episodes in a 1 yr)

Epidemiology
• lifetime prevalence: 1% BPI, 1.1% BPII, 2.4% Subthreshold BPD; M:F = 1:1
• age of onset: teens to 20s, usually MDE first, manic episode 6-10 years after, average age of first manic episode 32 yr

Risk Factors
• genetic: 60-65% of bipolar patients have family history of major mood disorders, especially bipolar disorders
• clinical features predictive of bipolar > unipolar diagnosis given history of MDE: early age of onset (<25 yr), increased number of MDEs, psychotic symptoms, postpartum onset, anxiety disorders (especially separation, panic), antidepressant failure due to early “poop out” or hypomanic symptoms, early impulsivity and aggression, substance abuse, cyclothymic temperament

Treatment
• lifestyle: psychoeducation for patient and supports on cycling nature of illness, ensure regular check ins, develop early warning system, “emergency plan” for manic episodes, promote stable routine (sleep, meals, exercise)
• biological: lithium, anticonvulsants, antipsychotics, ECT (if refractory); monotherapy with antidepressants should be avoided
  • mood stabilizers vary in their ability to “treat” (reduce symptoms acutely) or “stabilize” (prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy is common
  • treating mania: lithium, valproate, carbamazepine (2nd line), SGA, ECT, benzodiazepines (for acute agitation)
  • preventing mania: same as above but usually at lower dosages, minus benzodiazepines
  • treating depression: lithium, lurasidone, quetiapine, lamotrigine, antidepressants (only with mood stabilizer), ECT
  • preventing depression: same as above plus aripiprazole, valproate (note: quetiapine first line in treating bipolar II depression)
  • mixed episode or rapid cycling: multi-agent therapy, lithium or valproate + SGA (lurasidone, aripiprazole, olanzapine)
• psychological: supportive or psychodynamic psychotherapy, CBT, IPT or interpersonal social rhythm therapy, family therapy
• social: vocational rehabilitation, consider leave of absence from school/work, assess capacity to manage finances, drug and EtOH cessation, sleep hygiene, social skills training, education and recruitment of family members

Course and Prognosis
• high suicide rate (15% mortality from suicide), especially in mixed states
• BP I and II are chronic conditions with a relapsing and remitting course featuring alternating manic and depressive episodes; depressive symptoms tend to occur more frequently and last longer than manic episodes
• can achieve high level of functioning between episodes
• may switch rapidly between depression and mania without any period of euthymia in between
• high recurrence rate for mania – 90% will have a subsequent episode in the next 5 yr
• long term follow up of BP I – 15% well, 45% well with relapses, 30% partial remission, 10% chronically ill

CYCLOTHYMIA

Diagnosis
• presence of numerous periods of hypomanic and depressive symptoms (not meeting criteria for full hypomanic episode or MDE) for ≥2 yr; never without symptoms for >2 mo
• never have met criteria for MDE, manic or hypomanic episodes
• symptoms are not due to the direct physiological effects of a substance or GMC
• symptoms cause clinically signifcant distress or impairment in social, occupational, or other important areas of functioning

Treatment
• similar to Bipolar I: mood stabilizer ± psychotherapy, avoid antidepressant monotherapy, treat any comorbid substance use disorder

Anxiety Disorders

Definition
• anxiety is a universal human characteristic involving tension, apprehension, or even terror
• serves as an adaptive mechanism to warn about an external threat by activating the sympathetic nervous system (fight or flight)
• manifestations of anxiety can be described through
  • physiology: main brain structure involved is the amygdala (fear conditioning);
    neurotransmitters involved include 5-HT, cholecystokinin, epinephrine, norepinephrine, DA
  • psychology: one’s perception of a given situation is distorted which causes one to believe it is threatening in some way
  • behaviour: once feeling threatened, one responds by escaping or facing the situation, thereby causing a disruption in daily functioning
• anxiety becomes pathological when:
  • fear is greatly out of proportion to risk/severity of threat
  • response continues beyond existence of threat or becomes generalized to other similar or dissimilar situations
  • social or occupational functioning is impaired
  • often comorbid with substance use and depression

Differential Diagnosis

Table 2. Differential Diagnosis of Anxiety Disorders

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>Post-MI, arrhythmia, congestive heart failure, pulmonary embolus, mitral valve prolapse</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Asthma, COPD, pneumonia, hyperventilation</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hyperthyroidism, pheochromocytoma, hypoglycemia, hyperadrenalism, hyperparathyroidism</td>
</tr>
<tr>
<td>Metabolic</td>
<td>Vitamin B12 deficiency, porphyria</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Neoplasm, vestibular dysfunction, encephalitis</td>
</tr>
<tr>
<td>Substance-Induced</td>
<td>Intoxication (caffeine, amphetamines, cocaine, thyroid preparations, OTC for colds/ decongestants), withdrawal (benzodiazepines, alcohol)</td>
</tr>
<tr>
<td>Other Psychiatric Disorders</td>
<td>Psychotic disorders, mood disorders, personality disorders (OCD), somatoform disorders</td>
</tr>
</tbody>
</table>

Medical Workup of Anxiety Disorder
• routine screening: physical exam, CBC, thyroid function test, electrolytes, urinalysis, urine drug screening
• additional screening: neurological consultation, chest X-ray, ECG, CT head
### Panic Disorder

**DSM-5 Diagnostic Criteria for Panic Disorder**
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A. recurrent unexpected panic attacks - a panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes, and during which time four (or more) of the following symptoms occur
- palpitations, pounding heart, or accelerated heart rate
- sweating
- trembling or shaking
- sensations of shortness of breath or smothering
- feelings of choking
- chest pain or discomfort
- nausea or abdominal distress
- feeling dizzy, unsteady, light-headed, or faint
- chills or heat sensations
- paresthesias (numbness or tingling sensations)
- derealization (feeling of unreality) or depersonalization (being detached from oneself)
- fear of losing control or "going crazy"
- fear of dying

B. 1 mo (or more) of “anxiety about panic attacks” - at least one of the attacks has been followed by one or both of the following:
- persistent concern or worry about additional panic attacks or their consequences
- a significant maladaptive change in behaviour related to the attacks

C. the disturbance is not attributable to the physiological effects of a substance or another medical condition

D. the disturbance is not better explained by another mental disorder

**Epidemiology**
- prevalence: 2-5% (one of the top five most common reasons to see a family doctor); M:F = 1:2-3
- onset: average early-mid 20s, familial pattern

**Treatment**
- psychological
  - CBT: interoceptive exposure (eliciting symptoms of a panic attack and learning to tolerate the symptoms without coping strategies); cognitive restructuring (addressing underlying beliefs regarding the panic attacks), relaxation techniques (visualization, box-breathing)
- pharmacological
  - SSRIs: fluoxetine, citalopram, paroxetine, fluvoxamine, sertraline
  - SNRI: venlafaxine
  - with SSRIs/SNRIs start with low doses, titrate up slowly
  - anxiety disorders often require treatment at higher doses for a longer period of time than depression (i.e. full response may take up to 12 wk)
  - to prevent non-compliance due to physical side effects, explain symptoms to expect prior to initiation of therapy
  - other antidepressants (mirtazapine, MAOIs)
    - consider avoiding bupropion or TCAs due to stimulating effects (exacerbate anxious symptoms)
  - benzodiazepines (short-term, low dose, regular schedule, long half-life, avoid prn usage)

**Prognosis**
- 6-10 yr post-treatment: 30% well, 40-50% improved, 20-30% no change or worse
- clinical course: chronic, but episodic with psychosocial stressors

### Agoraphobia

**DSM-5 Diagnostic Criteria for Agoraphobia**
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• “Anxiety about not being able to escape, > 6 mo”

A. marked fear or anxiety about two (or more) of the following five situations:
- using public transportation
- being in open spaces
- being in enclosed places
- standing in line or being in a crowd
- being outside of the home alone

B. the individual fears or avoids these situations because of thoughts that escape might be difficult or help might not be available in the event of developing panic-like symptoms or other incapacitating or embarrassing symptoms
C. the agoraphobic situations almost always provoke fear or anxiety
D. the agoraphobic situations are actively avoided, require the presence of a companion, or are endured with intense fear or anxiety
E. the fear or anxiety is out of proportion to the actual danger posed by the agoraphobic situations and to the sociocultural context
F. the fear, anxiety, or avoidance is persistent, typically lasting ≥6 mo
G. the fear, anxiety, or avoidance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning
H. if another medical condition is present, the fear, anxiety, or avoidance is clearly excessive
I. the fear, anxiety, or avoidance is not better explained by the symptoms of another mental disorder and are not related exclusively to obsessions, perceived defects or flaws in physical appearance, reminders of traumatic events, or fear of separation

Note: agoraphobia is diagnosed irrespective of the presence of panic disorder. If an individual's presentation meets criteria for panic disorder and agoraphobia, both diagnoses should be assigned

Treatment
• as per panic disorder

Generalized Anxiety Disorder

DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder
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A. excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 mo, about a number of events or activities (such as work or school performance)
B. the individual finds it difficult to control the worry
C. the anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 mo)
1. restlessness or feeling keyed up or on edge
2. being easily fatigued
3. difficulty concentrating or mind going blank
4. irritability
5. muscle tension
6. sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep)
D. the anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning
E. the disturbance is not attributable to the physiological effects of a substance or another medical condition
F. the disturbance is not better explained by another mental disorder

Epidemiology
• 1 yr prevalence: 3-8%; M:F = 1:2
• if considering only those receiving inpatient treatment, ratio is 1:1
• most commonly presents in early adulthood

Treatment
• lifestyle: caffeine and EtOH avoidance, sleep hygiene
• psychological: CBT including relaxation techniques, mindfulness
• biological
  ▪ SSRIs and SNRIs are 1st line (paroxetine, escitalopram, sertraline, venlafaxine XL)
  ▪ 2nd line: buspirone (tid dosing), bupropion (caution due to stimulating effects),
  ▪ add-on benzodiazepines (short-term, low dose, regular schedule, long half-life, avoid prn usage)
  ▪ β-blockers not recommended

Prognosis
• chronically anxious adults become less so with age
• depends on pre-morbid personality functioning, stability of relationships, work, and severity of environmental stress
• difficult to treat

Phobic Disorders

Specific Phobia
• definition: marked and persistent (> 6 mo) fear that is excessive or unreasonable, cued by presence or anticipation of a specific object or situation
• lifetime prevalence 12-16%; M:F ratio variable
• types: animal/insect, environment (heights, storms), blood/injection/injury, situational (airplane, closed spaces), other (loud noise, clowns)
Social Phobia (Social Anxiety Disorder)
- **Definition**: marked and persistent (> 6 mo) fear of social or performance situations in which one is exposed to unfamiliar people or to possible scrutiny by others; fearing he/she will act in a way that may be humiliating or embarrassing (e.g. public speaking, initiating or maintaining conversation, dating, eating in public)
- **12 month prevalence rate may be as high as 7%; M:F ratio approximately equal**

Diagnostic Criteria for Phobic Disorders
- exposure to stimulus almost invariably provokes an immediate anxiety response; may present as a panic attack
- person recognizes fear as excessive or unreasonable
- situations are avoided or endured with anxiety/distress
- significant interference with daily routine, occupational/social functioning, and/or marked distress

Treatment
- **psychological**
  - cognitive behaviour therapy (focusing on both in vivo and virtual exposure therapy, gradually facing feared situations)
  - behavioural therapy is more efficacious than medication
- **biological**
  - SSRIs/SNRIs (e.g. fluoxetine, paroxetine, sertraline, venlafaxine), MAOIs
  - β-blockers or benzodiazepines in acute situations (e.g. public speaking)

Prognosis
- chronic

### Obsessive-Compulsive Disorder

**DSM-5 Diagnostic Criteria for Obsessive-Compulsive Disorder**
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A. **presence of obsessions, compulsions, or both**
   - obsessions are defined by (1) and (2)
     1. recurrent and persistent thoughts, urges, or images that are experienced, at some time during the disturbance, as intrusive and unwanted, and cause marked anxiety or distress in most individuals
     2. the individual attempts to ignore or suppress such thoughts, urges, or images, or to neutralize them with some other thought or action (i.e. by performing a compulsion; see below)
   - compulsions are defined by (1) and (2)
     1. repetitive behaviours (e.g. hand washing, ordering, checking) or mental acts (e.g. praying, counting, repeating words silently) that the individual feels driven to perform in response to an obsession or according to rules that must be applied rigidly
     2. behaviours mental acts are aimed at preventing or reducing anxiety or distress, or preventing some dreaded event or situation; however, these behaviours or mental acts are not connected in a realistic way with what they are designed to neutralize or prevent, or are clearly excessive

B. the obsessions or compulsions are time-consuming (e.g. take >1 h/d) or cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. the obsessive-compulsive symptoms are not attributable to the physiological effects

D. the disturbance is not better explained by the symptoms of another mental disorder

**Epidemiology**
- 12 mo prevalence 1.1-1.8%; females affected at slightly higher rates than males
- rate of OCD in first-degree relatives is higher than in the general population

**Treatment**
- CBT: exposure with response prevention (ERP) – involves exposure to feared situations with the addition of preventing the compulsive behaviours; cognitive strategies include challenging underlying beliefs
- pharmacotherapy: SSRIs/SNRIs (12-16 week trials, higher doses vs. depression), clomipramine; adjunctive antipsychotics (risperidone)

**Prognosis**
- tends to be refractory and chronic
Trauma- and Stressor-Related Disorders

Post-Traumatic Stress Disorder

DSM-5 Diagnostic Criteria for Post-Traumatic Stress Disorder

A. exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways
   1. directly experiencing the traumatic event(s)
   2. witnessing, in person, the event(s) as it occurred to others
   3. learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental
   4. experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g. first responders collecting human remains: police officers repeatedly exposed to details of child abuse)

B. presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred
   1. recurrent, involuntary, and intrusive distressing memories of the traumatic event(s)
   2. recurrent distressing dreams in which the content and/or affect of the dream are related to the traumatic event(s)
   3. dissociative reactions (e.g. flashbacks) in which the individual feels or acts as if the traumatic event(s) were occurring
   4. intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
   5. marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)

C. persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following
   1. avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)
   2. avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s)

D. negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following
   1. inability to remember an important aspect of the traumatic event(s)
   2. persistent and exaggerated negative beliefs or expectations about oneself, others, or the world
   3. persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others
   4. persistent negative emotional state (e.g. fear, horror, anger, guilt, or shame)
   5. markedly diminished interest or participation in significant activities
   6. feelings of detachment or estrangement from others
   7. persistent inability to experience positive emotions

E. marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following
   1. irritable behaviour and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
   2. reckless or self-destructive behaviour
   3. hypervigilance
   4. exaggerated startle response
   5. problems with concentration
   6. sleep disturbance (e.g. difficulty falling or staying asleep or restless sleep)

F. duration of the disturbance (criteria B, C, D, and E) is more than 1 mo

G. the disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning

H. the disturbance is not attributable to the physiological effects of a substance or another medical condition

Epidemiology
- prevalence of 7% in general population
- men's trauma is most commonly combat experience/physical assault; women's trauma is usually physical or sexual assault

Treatment
- psychotherapy, CBT
  - ensure safety and stabilize: e.g. emotional regulation techniques (e.g. breathing, relaxation)
  - once coping mechanisms established, can explore/mourn trauma - challenge dysfunctional beliefs, etc.
  - reconnect and integrate - exposure therapy, etc.

Acute Stress Disorder
- May be a precursor to PTSD
- Similar symptoms to PTSD
- Symptoms persist 3 d after a trauma until 1 mo after the exposure
• biological  
  † SSRIs (e.g. paroxetine, sertraline)  
  † prazosin (for treating disturbing dreams and nightmares)  
  † benzodiazepines (for acute anxiety)  
  † adjunctive atypical antipsychotics (risperidone, olanzapine)  
• eye movement desensitization and reprocessing (EMDR): an experimental method of reprocessing memories of distressing events by recounting them while using a form of dual attention stimulation such as eye movements, bilateral sound, or bilateral tactile stimulation (its use is controversial because of limited evidence)

Complications  
• substance abuse, relationship difficulties, depression, impaired social and occupational functioning disorders, personality disorders

Adjustment Disorder  
• a versatile clinical entity designed to capture patients who have difficulty coping with a stressful life event or situation and develop acute, often transient, emotional or behavioural symptoms that resemble less severe versions of other psychiatric conditions

DSM-5 Diagnostic Criteria for Adjustment Disorder  
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A. the development of emotional or behavioural symptoms in response to an identifiable stressor(s) occurring within 3 mo of the onset of the stressor(s)  
B. these symptoms or behaviours are clinically significant as evidenced by either of the following:  
  † marked distress that is in excess of what would be expected from exposure to the stressor  
  † significant impairment in social or occupational (academic) functioning  
C. the stress-related disturbance does not meet criteria for another mental disorder and is not merely an exacerbation of a pre-existing mental disorder  
D. the symptoms do not represent normal bereavement  
E. once the stressor (or its consequences) has terminated, the symptoms do not persist for more than an additional 6 mo  
  † specifiers: with depressed mood, with anxiety, with mixed anxiety/depression, with conduct disturbance, with mixed disturbance of conduct/emotions, unspecified

Classification  
• types of stressors  
  † single (e.g. termination of romantic relationship)  
  † multiple (e.g. marked business difficulties and marital problems)  
  † recurrent (e.g. seasonal business crises)  
  † continuous (e.g. living in a crime-ridden neighbourhood)  
  † developmental events (e.g. going to school, leaving parental home, getting married, becoming a parent, failing to attain occupational goals, retirement)

Epidemiology  
• F:M 2:1, prevalence 2-8% of the population

Treatment  
• brief psychotherapy: individual or group (particularly useful for patients dealing with unique and specific medical issues; e.g. colostomy or renal dialysis groups), crisis intervention  
• biological  
  † benzodiazepines may be used for those with significant anxiety symptoms (short-term, low-dose, regular schedule)

Bereavement

Clinical Presentation  
• bereavement is a normal psychological and emotional reaction to a significant loss, also called grief or mourning  
• length and characteristics of “normal” bereavement are variable between individuals/cultures; however, there are general commonalities in the symptoms, course and expected resolution that allow clinicians to monitor for abnormal severity  
• normal response: protest → searching and acute anguish → despair and detachment → reorganization  
• if a patient meets criteria for MDD, even in the context of a loss or bereavement scenario, they are still diagnosed with MDD  
• presence of the following symptoms may indicate abnormal grief/presence of MDD  
  † guilt about things other than actions taken or not taken by the survivor at the time of death  
  † thoughts of death other than the survivor feeling that they would be better off dead or should have died with the deceased person; morbid preoccupation with worthlessness

Risk Factors for Poor Bereavement Outcome  
• Poor social supports  
• Unanticipated death or lack of preparation for death  
• Highly dependent relationship with deceased  
• High initial distress  
• Other concurrent stresses and losses  
• Death of a child  
• Pre-existing psychiatric disorders, especially depression and separation anxiety
marked psychomotor retardation; prolonged and marked functional impairment
hallucinatory experiences other than thinking that the survivor hears the voice of or
transiently sees the image of the deceased person
dysphoria that is pervasive and independent of thoughts or triggers of the deceased, absence
of mood reactivity
after 12 mo, if patient continues to yearn/long for the deceased, experience intense sorrow/
emotional pain in response to the death, remain preoccupied with the deceased or with their
circumstance of death, then may start to consider a diagnosis of “persistent complex bereavement
disorder”

Treatment
• support and watchful waiting should be first line, as well as education and normalization of the
grief process
• screen for increased alcohol, cigarette and drug use
• normal grief should not be treated with antidepressant or antianxiety medication, as it is important
to allow the person to experience the whole mourning process to achieve resolution
• psychosocial: for those needing additional support, complex grief/bereavement, or significant
MDD, grief therapy (individual or group) is indicated
• pharmacotherapy: MDD present, past history of mood disorders, severe or autonomous symptoms

Neurocognitive Disorders

Delirium
• see Neurology, N21 and Geriatric Medicine, GM3

DSM-5 Diagnostic Criteria for Delirium
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A. attention and awareness: disturbance in attention (i.e. reduced ability to direct, focus, sustain,
and shift attention) and awareness (reduced orientation to the environment)
B. acute and fluctuating: disturbance develops over short period of time (usually hours to days),
represents a change from baseline attention and awareness, and tends to fluctuate in severity
during the course of a day
C. cognitive changes: an additional disturbance in cognition (e.g. memory deficit, disorientation,
language, visuospatial ability, or perception)
D. not better explained: disturbances in criteria A and C are not better explained by another
neurocognitive disorder (pre-existing, established, or evolving) and do not occur in the context
of a severely reduced level of arousal (e.g. coma)
E. direct physiological cause: evidence that disturbance is a direct physiological consequence of
another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or
medication), toxin, or is due to multiple etiologies
• Note: can have HYPERactive, HYPOPactive, or MIXED presentation

Clinical Presentation and Assessment
• common symptoms
  ▪ distractibility, disorientation (time, place, rarely person)
  ▪ misinterpretations, illusions, hallucinations
  ▪ speech/language disturbances (dysarthria, dysnomia, dysgraphia)
  ▪ affective symptoms (anxiety, fear, depression, irritability, anger, euphoria, apathy)
  ▪ shifts in psychomotor activity (gropping/picking at clothes, attempts to get out of bed when
unsafe, sudden movements, sluggishness, lethargy)
  ▪ Folstein Mini Mental Status Exam is helpful to assess baseline of altered mental state (i.e. score will
improve as symptoms resolve)

Risk Factors
• hospitalization (incidence 10-56%)
• previous delirium
• nursing home residents (incidence 60%)
• polypharmacy (e.g. anticholinergic)
• old age (especially males)
• severe illness (e.g. cancer, AIDS)
• recent anesthesia or surgery
• substance abuse
• pre-existing cognitive impairment, brain pathology, psychiatric illness

Etiology
• Infectious (encephalitis, meningitis, UTI, pneumonia)
• Withdrawal (alcohol, barbiturates, benzodiazepines)
• Acute metabolic disorder (electrolyte imbalance, hepatic or renal failure)
• Trauma (head injury, post-operative)

Bereavement is associated with a significant increase in morbidity and mortality acutely following the loss, with
effects seen up to 1 yr after
Loneliness is the most common symptom that continues to persist
in normal bereavement and may last several years
Confusion Assessment Method (CAM) for Diagnosis of Delirium
Highly sensitive and specific method to
diagnosis delirium
Part 1: an assessment instrument that
screens for overall cognitive impairment.
Part 2: includes four features found best able to distinguish delirium from other
cognitive impairments
Need (1) + (2) + (3 or 4)
(1) Acute onset and fluctuating course
(2) Inattention
(3) Disorganized thinking
(4) Altered level of consciousness -
hyperactive or hypoactive
Visual hallucinations are organic until
proven otherwise
• CNS pathology (stroke, hemorrhage, tumour, seizure disorder, Parkinson’s)
• Hypoxia (anemia, cardiac failure, pulmonary embolus)
• Deficiencies (vitamin B₁₂, folic acid, thiamine)
• Endocrinopathies (thyroid, glucose, parathyroid, adrenal)
• Acute vascular (shock, vasculitis, hypertensive encephalopathy)
• Toxins: substance use, sedatives, opioids (especially morphine), anesthetics, anticholinergics, anticonvulsants, dopaminergic agents, steroids, insulin, glyburide, antibiotics (especially quinolones), NSAIDs
• Heavy metals (arsenic, lead, mercury)

Investigations
• standard: CBC and differential, electrolytes, Ca²⁺, PO₄³⁻, Mg²⁺, glucose, ESR, LFTs, Cr, BUN, TSH, vitamin B₁₂, folate, albumin, urine C&S, R&M
• as indicated: ECG, CXR, CT head, toxicology/heavy metal screen, VDRL, HIV, LP, blood cultures, EEG (typically abnormal - generalized slowing or fast activity, can also be used to rule out underlying seizures or post-ictal states as etiology)
• indications for CT head: focal neurological deficit, acute change in status, anticoagulant use, acute incontinence, gait abnormality, history of cancer

Management
• intrinsic
  ▪ identify and treat underlying cause immediately
  ▪ stop all non-essential medications
  ▪ maintain nutrition, hydration, electrolyte balance and monitor vitals
• extrinsic
  ▪ environment: quiet, well-lit, near window for cues regarding time of day
  ▪ optimize hearing and vision
  ▪ room near nursing station for closer observation; constant care if patient jumping out of bed, pulling out lines
  ▪ family member present for reassurance and re-orientation
  ▪ frequent orientation - calendar, clock, reminders
• biological
  ▪ low dose, high potency antipsychotics: haloperidol has the most evidence; reasonable alternatives include risperidone, olanzapine (more sedating, less QT prolongation), quetiapine (if EPS), aripiprazole
  ▪ benzodiazepines only to be used in alcohol withdrawal delirium; otherwise, can worsen delirium
  ▪ try to minimize anticholinergic side effects
  ▪ physical restraints if patient becomes violent

Prognosis
• up to 50% 1 yr mortality rate after episode of delirium

Major Neurocognitive Disorder (Dementia)

• see Neurology, N22

DSM-5 Diagnostic Criteria for Major Neurocognitive Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. evidence of significant cognitive decline from a previous level of performance in one or more cognitive domains (complex attention, executive function, learning and memory, language, perceptual-motor, or social cognition) based on
  1. concern of the individual, a knowledgeable informant, or the clinician that there has been a significant decline in cognitive function;
  2. substantial impairment in cognitive performance, preferably documented by standardized neuropsychological testing or, in its absence, another quantified clinical assessment
B. cognitive deficits interfere with independence in everyday activities (i.e. at a minimum, requiring assistance with complex instrumental activities of daily living such as paying bills or managing medications)
  ▪ Note: if do not interfere in B, and impairments are mild-moderate in A, considered “mild neurocognitive disorder”; see Neurology, N21

C. cognitive deficits do not occur exclusively in the context of a delirium
D. cognitive deficits are not better explained by another mental disorder (e.g. major depressive disorder, schizophrenia)

Dosing for Haloperidol in Delirium
Typical dose 0.5-1 mg
Dosing schedule varies with clinical approach: PRN often used, but QHS or QHS and QAM also employed to account for hypoactive delirium, which is otherwise often missed

The 4 As of Dementia
A - Amnesia
A - Aphasia
A - Apraxia
A - Agnosia

The “Mini Cog” Rapid Assessment
• 3 word recall
• Clock drawn to “10 past 11”
• Animal lists
Specify whether due to

<table>
<thead>
<tr>
<th>Neurocognitive Disorder</th>
<th>Traumatic brain injury</th>
<th>Substance/medication use</th>
<th>Huntington’s disease</th>
<th>Another medical condition</th>
<th>Multiple etiologies</th>
<th>Unspecified</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s disease</td>
<td>Substantive illness</td>
<td>HIV infection</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frontotemporal lobar degeneration</td>
<td></td>
<td>Proinflammatory disease</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lewy body disease</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Vascular disease</td>
<td></td>
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<tr>
<td>Normal pressure hydrocephalus</td>
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</tbody>
</table>

Epidemiology
- prevalence increases with age: 10% in patients >65 yr of age; 25% in patients >85 yr of age
- prevalence is increased in people with Down’s syndrome and head trauma
- Alzheimer’s disease comprises >50% of cases; vascular causes comprise approximately 15% of cases (other causes of dementia neurocognitive disorder – see Neurology, N25-N27)
- average duration of illness from onset of symptoms to death is 8-10 yr

Subtypes
- with or without behavioural disturbance (e.g. wandering, agitation)
- early-onset: age of onset <65 yr
- late-onset: age of onset >65 yr

Investigations (rule out reversible causes)
- standard: see Delirium, PS20
- as indicated: VDRL, HIV, SPECT, CT head in dementia
- indications for CT head: same as for delirium, plus: age <60, rapid onset (unexplained decline in cognition or function over 1-2 mo), dementia of relatively short duration (<2 yr), recent significant head trauma, unexplained neurological symptoms (new onset of severe headache/seizures)

Management
- see Neurology, N22 for further management
- treat underlying medical problems and prevent others
- provide orientation cues for patient (e.g. clock, calendar)
- provide education and support for patient and family (e.g. day programs, respite care, support groups, home care)
- consider long-term care plan (nursing home) and power of attorney/living will
- inform Ministry of Transportation about patient’s inability to drive safely
- consider pharmacological therapy
  - cholinesterase inhibitors (e.g. donepezil [Aricept®], rivastigmine, galantamine) for mild to severe disease
  - NMDA receptor antagonist (e.g. memantine) for moderate to severe disease
  - low-dose neuroleptics (e.g. risperidone, quetiapine), antidepressants or trazodone if behavioural or emotional symptoms prominent – start low and go slow
  - reassess pharmacological therapy every 3 mo

Table 3. Comparison of Dementia, Delirium, and Pseudodementia of Depression

<table>
<thead>
<tr>
<th>Dementia/Major Neurocognitive Disorder</th>
<th>Delirium</th>
<th>Pseudodementia of Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Gradual/step-wise decline</td>
<td>Acute (h-d)</td>
</tr>
<tr>
<td>Duration</td>
<td>Months-years</td>
<td>Days-weeks</td>
</tr>
<tr>
<td>Natural History</td>
<td>Progressive</td>
<td>Fluctuating, reversible</td>
</tr>
<tr>
<td></td>
<td>Usually irreversible</td>
<td>High morbidity/mortality in very old</td>
</tr>
<tr>
<td>Level of Consciousness</td>
<td>Normal</td>
<td>Fluctuating (over 24 h)</td>
</tr>
<tr>
<td>Attention</td>
<td>Not initially affected</td>
<td>Decreased (wandering, easy distraction)</td>
</tr>
<tr>
<td>Orientation</td>
<td>Intact initially</td>
<td>Impaired (usually to time and place), fluctuates</td>
</tr>
<tr>
<td>Behaviour</td>
<td>Disinhibition, impairment in ADL/ADL, personality change, loss of social graces</td>
<td>Severe agitation/retardation</td>
</tr>
<tr>
<td>Psychomotor</td>
<td>Normal</td>
<td>Fluctuates between extremes</td>
</tr>
<tr>
<td>Sleep Wake Cycle</td>
<td>Fragmented sleep at night</td>
<td>Reversed sleep wake cycle</td>
</tr>
<tr>
<td>Mood and Affect</td>
<td>Labile but not usually anxious</td>
<td>Anxious, irritable, fluctuating</td>
</tr>
<tr>
<td>Cognition</td>
<td>Decreased executive functioning, paucity of thought changes</td>
<td>Fluctuating preceded by mood changes</td>
</tr>
<tr>
<td>Memory Loss</td>
<td>Recent, eventually remote</td>
<td>Marked recent</td>
</tr>
<tr>
<td>Language</td>
<td>Agraphia, aphasia, decreased comprehension, repetition, speech (echolalia, palilalia)</td>
<td>Dysnomia, dysgraphia, speech rambling, irrelevant, incoherent, subject changes</td>
</tr>
<tr>
<td>Delusions</td>
<td>Compensatory</td>
<td>Nightmarish and poorly formed</td>
</tr>
<tr>
<td>Hallucinations</td>
<td>Variable</td>
<td>Visual common</td>
</tr>
<tr>
<td>Quality of Hallucinations</td>
<td>Vacuum/blind</td>
<td>Frightening/bizarre</td>
</tr>
<tr>
<td>Medical Status</td>
<td>Variable</td>
<td>Acute illness, drug toxicity</td>
</tr>
</tbody>
</table>
Substance-Related and Addictive Disorders

• a neurobiological disorder involving compulsive drug seeking and drug taking, despite adverse consequences, with loss of control over drug use (think issues with the "3 Cs": compulsive, consequences, control)

Overview
• dependence is the hallmark of substance use disorders and comes in the following forms:
  ▪ behavioural: substance-seeking activities and pathological use patterns
  ▪ physical: physiologic withdrawal effects without use
  ▪ psychological: continuous or intermittent cravings for the substance to avoid dysphoria or attain drug state
• abuse: drug use that deviates from the approved social or medical pattern, usually causing impairment or disruption to function in self or others
• these disorders are usually chronic with a relapsing and remitting course

Epidemiology
• 47% of those with substance abuse have mental health problems
• 29% of those with a mental health disorder have a substance use disorder
• 47% of those with schizophrenia and 25% of those with an anxiety disorder have a substance use disorder

Etiology
• almost all drugs (and activities) of abuse increase dopamine in the nucleus accumbens, an action that contributes to their euphoric properties and, with repeated use, to their ability to change signalling pathways in the brain's reward system
• substance use disorders arise from multifactorial interactions between genes (personality, neurobiology) and environment (low socioeconomic status, substance-using peers, abuse history, chronic stress)

Diagnosis
• substance use disorders are measured on a continuum from mild to severe based on the number of criteria met within 12 mo
  ▪ mild: 2-3
  ▪ moderate: 4-5
  ▪ severe: 6 or more
• each specific substance is meant to be addressed as a separate use disorder (e.g. a single patient may have moderate alcohol use disorder, and a mild stimulant use disorder) and diagnosed utilizing the same overarching criteria
• criteria for substance use disorders (PEC WITH MCAT)
  ▪ use despite Physical or psychological problem (e.g. alcoholic liver disease or cocaine related nasal problems)
  ▪ failures in important External roles at work/school/home
  ▪ Craving or a strong desire to use substance
  ▪ Withdrawal
  ▪ continued use despite Interpersonal problems
  ▪ Tolerance, needing to use more substance to get same effect
  ▪ use in physically Hazardous situations
  ▪ More substance used or for longer period than intended
  ▪ unsuccessful attempts to Cut down
  ▪ Activities given up due to substance
  ▪ excessive Time spent on using or finding substance

Classification of Substances

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Intoxication</th>
<th>Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depressants</td>
<td>Alcohol, opioids, barbiturates, benzodiazepines, GHB</td>
<td>Euphoria, slurred speech, disinhibition, confusion, poor coordination, coma (severe)</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines, methylphenidate, MDMA, cocaine</td>
<td>Euphoria, mania, psychomotor agitation, anxiety, psychosis (especially paranoia), insomnia, cardiovascular complications (stroke, MI, arrhythmias), seizure</td>
</tr>
<tr>
<td>Hallucinogens</td>
<td>LSD, mescaline, psilocybin, PCP, ketamine, ibogaine, salvia</td>
<td>Distortion of sensory stimuli and enhancement of feelings, psychosis (++ visual hallucinations), delirium, anxiety (panic), poor coordination</td>
</tr>
</tbody>
</table>
General Approach to Assessment
• must be appropriate to the patient's current state of change (see Population Health and Epidemiology, Health Promotion Strategies, PH7, for Prochaska's Stages of Change Model)
• patients will only change when the pain of change appears less than the pain of staying the same
• provider can help by providing psychoeducation (emphasize neurobiologic model of addiction), motivation, and hope
• principles of motivational interviewing (see Psychotherapy, PS43)
  - non-judgmental stance
  - space for patient to talk and reflect
  - offer accurate empathic reflections back to patient to help frame issues
• although not explicitly in the substance use disorder criteria, the following questions are important to characterize HPI and safety
  - when was the last time you used? how long can you go without using?
  - by what route (oral ingestion, insufflation, smoking, IV) do you usually use?
  - are there any triggers that you know will cause you to use?
  - how has your substance use affected your work, school, relationships?
  - substances can be very expensive, how do you support your drug use?
  - have you experienced medical or legal consequences of your use?
  - any previous attempts to cut down or quit, did you experience any withdrawal symptoms?

General Approach to Treatment
• encourage and offer referral to evidence based services
  - social: 12-step programs (alcoholics anonymous, narcotics anonymous), family education and support
  - psychological therapy: addiction counselling, motivational enhancement therapy (MET), CBT, contingency management, group therapy, family therapy, marital counseling
  - medical management (differs for substances): acute detoxification, pharmacologic agents to aid maintenance
• harm reduction whenever possible: safe-sex practices, avoid driving while intoxicated, avoiding substances with child care, safe needle practices/exchange, pill-testing kits, reducing tobacco use
• comorbid psychiatric conditions: many will resolve with successful treatment of the substance use disorder but patients who meet full criteria for another disorder should be treated for that disorder with psychological and pharmacologic therapies

Nicotine
• see Family Medicine, FM11

Alcohol
• see Family Medicine, FM13 and Emergency Medicine, ER54

History
• CAGE: validated screening questionnaire
  C ever felt the need to Cut down on drinking?
  A ever felt Annoyed at criticism of your drinking?
  G ever feel Guilty about your drinking?
  E ever need a drink first thing in morning (Eye opener)?
  • for men, a score of ≥2 is a positive screen; for women, a score of ≥1 is a positive screen
  • if positive CAGE, then assess further to distinguish between problem drinking and alcohol dependence

Table 4. Canada’s Low-Risk Alcohol Drinking Guidelines

<table>
<thead>
<tr>
<th>Moderate Drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men: 3 or less/d (≤15/wk)</td>
</tr>
<tr>
<td>Women: 2 or less/d (≤10/wk)</td>
</tr>
<tr>
<td>Elderly: 1 or less/d</td>
</tr>
</tbody>
</table>

Alcohol Intoxication
• legal limit for impaired driving is 10.6 mmol/L (50 mg/dL) reached by 2-3 drinks/h for men and 1-2 drinks/h for women
• coma can occur with >60 mmol/L (non-tolerant drinkers) and 90-120 mmol/L (tolerant drinkers)

Alcohol Withdrawal
• occurs within 12-48 h after prolonged heavy drinking and can be life-threatening
• alcohol withdrawal can be described as having 4 stages, however not all stages may be experienced
  - stage 1 (onset 12-18 h after last drink): “the shakes” tremor, sweating, agitation, anorexia, cramps, diarrhea, sleep disturbance
  - stage 2 (onset 7-48 h): alcohol withdrawal seizures, usually tonic-clonic, non-focal and brief
  - stage 3 (onset 48 h): visual, auditory, olfactory or tactile hallucinations

Confabulations: the fabrication of imaginary experiences to compensate for memory loss

Make sure to ask about other alcohols: mouthwash, rubbing alcohol, methanol, ethylene glycol, aftershave (may be used as a cheaper alternative)
stage 4 (onset 3-5 d): delirium tremens, confusion, delusions, hallucinations, agitation, tremors, autonomic hyperactivity (fever, tachycardia, HTN)
- course: almost completely reversible in young; elderly often left with cognitive deficits
- mortality rate 20% if untreated

Management of Alcohol Withdrawal
- monitor using the Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A) scoring system
  - areas of assessment include
    - physical (5): nausea and vomiting, tremor, agitation, paroxysmal sweats, headache/fullness in head
    - psychological/cognitive (2): anxiety, orientation/clouding of sensorium
    - perceptual (3): tactile disturbances, auditory disturbances, visual disturbances
  - all categories are scored from 0-7 (except: orientation/sensorium 0-4), maximum score of 67
  - mild <10, moderate 10-20, severe >20

Table 5. CIWA-A Scale Treatment Protocol for Alcohol Withdrawal

<table>
<thead>
<tr>
<th>Basic Protocol</th>
<th>Diazepam 20 mg PO q1-2h prn until CIWA-A &lt;10 points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Observe 1-2 h after last dose and re-assess on CIWA-A scale</td>
</tr>
<tr>
<td></td>
<td>Thiamine 100 mg IM then 100 mg PO OD for 3 d</td>
</tr>
<tr>
<td></td>
<td>Supportive care (hydration and nutrition)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>History of Withdrawal Seizures</th>
<th>Diazepam 20 mg PO q1h for minimum of three doses regardless of subsequent CIWA scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>If age &gt;65 or patient has severe liver disease, severe asthma or respiratory failure</td>
<td>Use a short acting benzodiazepine</td>
</tr>
<tr>
<td></td>
<td>Lorazepam PO/SL/IM 1-4 mg q1-2h</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If Hallucinations are present</th>
<th>Haloperidol 2-5 mg IM/PO q1-4h – max 5 doses/d or atypical antipsychotics (olanzapine, risperidone)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diazepam 20 mg x 3 doses as seizure prophylaxis (haloperidol lowers seizure threshold)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Admit to Hospital if</th>
<th>Still in withdrawal after &gt;80 mg of diazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delirium tremens, recurrent arrhythmias, or multiple seizures</td>
</tr>
<tr>
<td></td>
<td>Medically ill or unsafe to discharge home</td>
</tr>
</tbody>
</table>

Wernicke-Korsakoff Syndrome
- alcohol-induced amnestic disorders due to thiamine deficiency
- necrotic lesions: mammillary bodies, thalamus, brainstem
- Wernicke's encephalopathy (acute and reversible): triad of nystagmus (CN VI palsy), ataxia, and confusion
- Korsakoff’s syndrome (chronic and only 20% reversible with treatment): anterograde amnesia and confabulations; cannot occur during an acute delirium or dementia and must persist beyond usual duration of intoxication/withdrawal
- management
  - Wernicke’s: thiamine 100 mg PO OD x 1-2 wk
  - Korsakoff’s: thiamine 100 mg PO bid/tid x 3-12 mo

Treatment of Alcohol Use Disorder
- non-pharmacological
  - see General Approach to Treatment, PS24
- pharmacological
  - naltrexone (Revia®): opioid antagonist, shown to be successful in reducing the “high” associated with alcohol, moderately effective in reducing cravings, frequency or intensity of alcohol binges
  - disulfiram (Antabuse®): blocks oxidation of alcohol (blocks acetaldehyde dehydrogenase); with alcohol consumption, acetaldehyde accumulates to cause a toxic reaction (vomiting, tachycardia, death); if patient relapses, must wait 48 h before restarting Antabuse®; prescribed only when treatment goal is abstinence. RCT evidence is generally poor or negative
  - acamprosate (Campral®): NMDA glutamate receptor antagonist; useful in maintaining abstinence and decreasing cravings

Opioids
- types of opioids: heroin, morphine, oxycodone, Tylenol #3* (codeine), hydromorphone, fentanyl
- major risks associated with the use of contaminated needles: increased risk of hepatitis B and C, bacterial endocarditis, HIV/AIDS

Acute Intoxication
- direct effect on receptors in CNS resulting in decreased pain perception, sedation, decreased sex drive, nausea/vomiting, decreased GI motility (constipation and anorexia), and respiratory depression

Delirium Tremens (alcohol withdrawal delirium)
- Autonomic hyperactivity (diaphoresis, tachycardia, increased respiration)
- Hand tremor
- Insomnia
- Psychomotor agitation
- Anxiety
- Nausea or vomiting
- Tonic-clonic seizures
- Visual/tactile/auditory hallucinations
- Persecutory delusions

OxyNEO vs. OxyContin
As of 2012, OxyContin was no longer available in Canada and was replaced by a new formulation of oxycodone called OxyNEO. OxyNEO is reported to be more tamper-resistant than OxyContin as the tablet is more difficult to crush. Furthermore, if OxyNEO is crushed, and added to water, it forms a thick gel-like substance that cannot be easily injected.
Toxic Reaction
- typical syndrome includes shallow respirations, miosis, bradycardia, hypothermia, decreased level of consciousness
- management
  - ABCs
  - IV glucose
  - naloxone hydrochloride (Narcan®): 0.4 mg up to 2 mg IV for diagnosis
  - treatment: intubation and mechanical ventilation, ± naloxone drip, until patient alert without naloxone (up to >48 h with long-acting opioids)
- caution with longer half-life; may need to observe for toxic reaction for at least 24 h

Withdrawal
- symptoms: depression, insomnia, drug-craving, myalgias, nausea, chills, autonomic instability (lacrimation, rhinorrhea, piloerection)
- onset: 6-12 h; duration: 5-10 d
- complications: loss of tolerance (overdose on relapse), miscarriage, premature labour
- management: long-acting oral opioids (methadone, buprenorphine), α-adrenergic agonists (clonidine)

Cocaine
- street names: blow, C, coke, crack, flake, freebase, rock, snow
- alkaloid extracted from leaves of the coca plant; blocks presynaptic uptake of dopamine (causing euphoria), norepinephrine and epinephrine (causing vasospasm, HTN)
- self-administered by inhalation, insufflation, or intravenous route

Intoxication
- elation, euphoria, pressured speech, restlessness, sympathetic stimulation (e.g. tachycardia, mydriasis, sweating)
- prolonged use may result in paranoia and psychosis

Overdose
- medical emergency: HTN, tachycardia, tonic-clonic seizures, dyspnea, and ventricular arrhythmias
- treatment with IV diazepam to control seizures and propanolol or labetalol to manage HTN and arrhythmias

Withdrawal
- initial “crash” (1-48 h): increased sleep, increased appetite
- withdrawal (1-10 wk): dysphoric mood plus fatigue, irritability, vivid unpleasant dreams, insomnia or hyperactivity, psychomotor agitation or retardation
- complications: relapse, suicide (significant increase in suicide during withdrawal period)
- management: supportive management

Treatment of Cocaine Use Disorder
- see General Approach to Treatment, PS24
- no pharmacologic agents have widespread evidence or acceptance of use

Complications
- cardiovascular: arrhythmias, MI, CVA, ruptured AAA
- neurologic: seizures
- psychiatric: psychosis, paranoia, delirium, suicidal ideation
- other: nasal septal deterioration, acute/chronic lung injury “crack lung”, possible increased risk of connective tissue disease
Amphetamines

- includes prescription medications for ADHD such as Ritalin® and Adderall®
- intoxication characterized by euphoria, improved concentration, sympathetic and behavioural hyperactivity and at high doses can mimic psychotic mania, can eventually cause coma
- chronic use can produce a paranoid psychosis which can resemble schizophrenia with agitation, paranoia, delusions and hallucinations
- withdrawal symptoms include dysphoria, fatigue, and restlessness
- treatment of amphetamine induced psychosis: antipsychotics for acute presentation, benzodiazepines for agitation, β-blockers for tachycardia, hypertension

Cannabis

- cannabis (marijuana) is the most commonly used illicit drug
- psychoactive substance: delta-9-tetrahydrocannabinol (Δ9-THC)
- intoxication characterized by tachycardia, conjunctival vascular engorgement, dry mouth, altered sensorium, increased appetite, increased sense of well-being, euphoria/laughter, muscle relaxation, impaired performance on psychomotor tasks including driving
- high doses can cause depersonalization, paranoia, anxiety and may trigger psychosis and schizophrenia if predisposed
- chronic use associated with tolerance and an apathetic, motivational state, increases risk of later manic episodes
- cessation following heavy use does produce a significant withdrawal syndrome: irritability, anxiety, insomnia, decreased food intake
- treatment of cannabis use disorder: see General Approach to Assessment, PS24

Hallucinogens

- types of hallucinogens by primary action
  - 5-HT2A agonists: LSD, mescaline (peyote), psilocybin mushrooms, DMT (ayahuasca)
  - NMDA antagonists: PCP, ketamine
  - μ-opioid agonists: salvia divinorum, ibogaine
  - 5-HT2A agonists are most commonly used, intoxication characterized by tachycardia, HTN, mydriasis, tremor, hyperpyrexia, and a variety of perceptual, mood and cognitive changes (rarely, if ever, deadly; treat vitals symptomatically)
- psychological effects of high doses: depersonalization, derealization, paranoia, and anxiety (panic with agoraphobia)
- tolerance develops rapidly (hours-days) to most hallucinogens so physical dependency is virtually impossible, although psychological dependency and problematic usage patterns can still occur
- chronic use associated with tolerance and an apathetic, motivational state, increases risk of later manic episodes
- support, reassurance, diminished stimulation; benzodiazepines or high potency antipsychotics seldom required (if used, use small doses), minimize use of restraints
- long term adverse effects: controversial role in triggering psychiatric disorders, particularly mood or psychosis, thought to be chiefly in individuals with genetic or other risk factors
- Hallucinogen Persisting Perception Disorder: DSM-5 diagnosis characterized by long lasting, spontaneous, intermittent recurrences of visual perceptual changes reminiscent of those experienced with hallucinogen exposure

“Club Drugs”

Table 6. The Mechanism and Effects of Common “Club Drugs”

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDMA (“Ecstasy”, “X”, “E”)</td>
<td>Acts on serotonergic and dopaminergic pathways, properties of a hallucinogen and stimulant</td>
<td>Enhanced sensorium; feelings of well-being, empathy</td>
<td>Sweating, tachycardia fatigue, muscle spasms (especially jaw clenching), ataxia, hyperthermia, arrhythmias, DIC, rhabdomyolysis, renal failure, seizures, death</td>
</tr>
<tr>
<td>Gamma Hydroxybutyrate (GHB, “G”, “Liquid Ecstasy”)</td>
<td>Biphasic dopamine response (inhibition then release) and releases opiate-like substance</td>
<td>Euphoric effects, increased aggression, impaired judgment</td>
<td>Sweating, tachycardia, fatigue, muscle spasms (especially jaw clenching), ataxia, severe withdrawal from abrupt cessation of high doses: tremor, seizures, psychosis</td>
</tr>
<tr>
<td>Flunitrazepam (Rohypnol®), “Roofies”, “Rope”, “The Forget Pill”</td>
<td>Potent benzdiazepine, rapid oral absorption</td>
<td>Sedation, psychomotor impairment, amnestic effects, decreased sexual inhibition</td>
<td>CNS depression with EtOH</td>
</tr>
<tr>
<td>Ketamine (“Special K”, “K-Ket”)</td>
<td>NMDA receptor antagonist, rapid-acting general anesthetic used in pediatrics and by veterinarians</td>
<td>“Dissociative” state, profound amnesia/anaesthesia, hallucinations and sympathomimetic effects</td>
<td>Psychological distress, accidents due to intensity of experience and lack of body control, in overdose, decreased LOC, respiratory depression, catatonia</td>
</tr>
</tbody>
</table>

Cannabinoid Hyperemesis Syndrome
An interesting and relatively new clinical phenomenon associated with chronic cannabis use characterized by cyclical, recurrent severe nausea, vomiting, and colicky pain. Possibly due to increased potency of available THC products. Patients often present to ED in acute distress with no evidence of specific GI pathology. Many patients will successfully self-medicate with hot baths or showers

Medical Uses of Marijuana
- Anorexia-cachexia (AIDS, cancer)
- Spasticity, muscle spasms (multiple sclerosis, spinal cord injury)
- Levodopa-induced dyskinesia (Parkinson’s Disease)
- Controlling tics and obsessive-compulsive behaviour (Tourette’s syndrome)
- Reducing intra-ocular pressure (glaucoma)

Cannabis Use and Risk of Psychotic or Affective Mental Health Outcomes: A Systematic Review
The Lancet 2007;370:119-129
Purpose: To review the evidence for cannabis use and occurrence of psychotic or affective mental health outcomes.
Study Characteristics: A meta-analysis of 35 population-based longitudinal studies, or case-control studies nested within longitudinal designs.
Results: There was an increased risk of any psychotic outcome in individuals who had ever used cannabis (pooled adjusted odds ratio = 1.41, 95% CI 1.20-1.65). Findings were consistent with a dose-response effect, with greater risk in people who used cannabis more frequently (2.09, 95% CI 1.54-2.64). Findings for depression, suicidal thoughts, and anxiety outcomes were less consistent. In both cases (psychotic and affective outcomes), a substantial confounding effect was present.
Conclusions: The findings are consistent with the view that cannabis increases risk of psychotic outcomes independent of transient intoxication effects, although evidence is less strong for affective outcomes. Although cannabis use and the development of psychosis are strongly associated, it is difficult to determine causality and it is possible that the association results from confounding factors or bias. The authors did conclude that there is sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life.

Emerging Medical Uses of Hallucinogens
Many hallucinogens are currently under investigation for therapeutic benefits; LSD & Psilocybin for end of life anxiety, MDMA for PTSD, Ketamine for rapid treatment of depression, ibogaine derivatives for addiction

Date Rape Drugs
- GHB
- Flunitrazepam (Rohypnol®)
- Ketamine
Table 6. The Mechanism and Effects of Common “Club Drugs” (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Effect</th>
<th>Adverse Effects</th>
</tr>
</thead>
</table>
| Methamphetamine   | Amphetamine stimulant, induces norepinephrine, dopamine, and serotonin release | Rush begins in min, effects last 6-8 h, increased activity, decreased appetite, general sense of well-being, tolerance occurs quickly, users often binge and crash | Short-term use: high agitation, rage, violent behaviour, occasionally hyperthermia and convulsions  
Long-term use: addiction, anxiety, confusion, insomnia, paranoia, auditory and tactile hallucinations (especially formication), delusions, mood disturbance, suicidal and homicidal thoughts, stroke, may be contaminated with lead, and IV users may present with acute lead poisoning |
| Phencyclidine      | Not understood, used by veterinarians to immobilize large animals          | Amnestic, euphoric, hallucinatory state                                                                                           | Horizontal/vertical nystagmus, myoclonus, ataxia, autonomic instability (treat with diazepam IV), prolonged agitated psychosis (treat with haloperidol); high risk for suicide; violence towards others; High dose can cause coma |

Somatic Symptom and Related Disorders

General Characteristics
- physical signs and symptoms lacking objective medical support in the presence of psychological factors that are judged to be important in the initiation, exacerbation, or maintenance of the disturbance
- cause significant distress or impairment in functioning
- symptoms are produced unconsciously and are not the result of malingering or factitious disorder, which are disorders of voluntary “faking” of symptoms (or intentionally inducing, e.g. injecting feces) for secondary gain
- primary gain: somatic symptom represents a symbolic resolution of an unconscious psychological conflict; serves to reduce anxiety and conflict with no external incentive
- secondary gain: the sick role; external benefits obtained or unpleasant duties avoided (e.g. work)

Management of Somatic Symptom and Related Disorders
- brief, regular scheduled visits with GP to facilitate therapeutic relationship and help patient feel cared for
- limit number of physicians involved in care, minimize medical investigations; coordinate necessary investigations
- emphasis on what the patient can change and control; the psychosocial coping skills, not their physical symptoms (functional recovery > explanation of symptoms)
- do not tell patient it is “all in their head,” emphasize these disorders are real entities or functional in nature
- psychotherapy: CBT, mindfulness interventions, biofeedback, conflict resolution
- minimize psychotropic drugs: anxiolytics in short-term only, antidepressants for comorbid depression and anxiety

Somatic Symptom Disorder

DSM-5 Diagnostic Criteria for Somatic Symptom Disorder
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association
A. one or more somatic symptoms that are distressing or result in significant disruption of daily life
B. excessive thoughts, feelings, or behaviours related to the somatic symptoms or associated health concerns as manifested by at least one of the following:
   1. disproportionate and persistent thoughts about the seriousness of one’s symptoms
   2. persistently high level of anxiety about health or symptoms
   3. excessive time and energy devoted to these symptoms or health concerns
C. although any one somatic symptom may not be continuously present, the state of being symptomatic is persistent (typically >6 mo)
- specify: With predominant pain (previously pain disorder) for those whose somatic symptom is primarily pain
- patients have physical symptoms and believe these symptoms represent the manifestation of a serious illness
- they will persist in this belief despite negative medical investigations and may develop different symptoms over time
- lifetime prevalence may be around 5-7% in the general adult population
- females tend to report more somatic symptoms than males do, cultural factors may influence sex ratio
- complications: anxiety and depression commonly comorbid (up to 80%), unnecessary medications or surgery
- often a misdiagnosis for an insidious illness so rule out all organic illnesses (e.g. multiple sclerosis)
**Illness Anxiety Disorder**

- preoccupation with fear of having, or the idea that one has, a serious disease, to the point of causing significant impairment
- convictions persist despite negative investigations and medical reassurance
- somatic symptoms are mild or not present
- there is a high level of anxiety about health and the individual is easily alarmed about personal health status
- person engages in maladaptive behaviour such as excessive physical checking or total healthcare avoidance
- duration is ≥6 mo; onset in 3rd-4th decade of life
- a new diagnostic entity so epidemiology is not well known; however, it is likely less common than SSD
- possible role for SSRIs due to generally high level of anxiety

**Conversion Disorder**

*(Functional Neurological Symptom Disorder)*

- one or more symptoms or deficits affecting voluntary motor or sensory function that mimic a neurological or GMC (e.g. impaired coordination, local paralysis, double vision, seizures, or convulsions)
- does not need to be preceded by a psychological event as per previous DSM criteria, however this is still worth exploring as many patients will present after such an event or related to a medical diagnosis in a first-degree relative
- 2-5/100,000 in general population; 5% of referrals to neurology clinics
- more common in rural populations and in individuals with little medical knowledge
- spontaneous remission in 95% of acute cases, 50% of chronic cases (>6 mo)
- key to diagnosis is specific neurological testing to detect incompatible findings (e.g. Hoover’s sign, dermatome testing)

Table 7. Differential of Somatic Symptom and Related Disorders

<table>
<thead>
<tr>
<th>Somatic Symptom Disorder</th>
<th>Illness Anxiety Disorder</th>
<th>Conversion Disorder</th>
<th>Factitious Disorder</th>
<th>Malingering</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present</td>
<td>Mild or absent</td>
<td>Neurologic, voluntary motor or sensory</td>
<td>Psychological or physical</td>
<td>Psychological or physical</td>
</tr>
<tr>
<td>Unconsciously Produced</td>
<td>Unconsciously</td>
<td>Unconsciously</td>
<td>Consciously</td>
<td>Consciously</td>
</tr>
<tr>
<td>Absent</td>
<td>Absent</td>
<td>Incompatible</td>
<td>Possible, attempts to falsify</td>
<td>Possible, attempts to falsify</td>
</tr>
</tbody>
</table>

**Dissociative Disorders**

**Definition**

- dissociation so severe that the usually integrated functions of consciousness and perception of self break down
- differential diagnosis: PTSD, acute stress disorder, borderline personality disorder, somatization disorder, substance abuse, GMC (various neurologic disorders including complex/partial seizures, migraine, Cotard syndrome)

**Dissociative Identity Disorder**

- disruption of identity characterized by two or more distinct personality states or an experience of possession
- can manifest as sudden alterations in sense of self and agency (ego-dysytonic emotions, behaviours, speech)
- features recurrent episodes of amnesia (declarative or procedural)
Dissociative Amnesia

- inability to recall important autobiographical information, usually of a traumatic or stressful nature, that is inconsistent with normal forgetting. Not attributable to other psychiatric disorder or medical illness
- localized/selective amnesia: failure to recall all/some events during a prescribed period of time
- generalized amnesia: (more rare) complete loss of memory for one’s life history, ± procedural, semantic knowledge. Usually sudden onset. Often will present with perplexity, disorientation, aimless wandering

Depersonalization/Derealization Disorder

- persistent or recurrent episodes of one or both of
  - depersonalization: experiences of detachment from oneself, feelings of unreality, or being an outside observer to one’s thoughts, feelings, speech, and actions (can feature distortions in perception including time, as well as emotional and physical numbing)
  - derealization: experiences of unreality or detachment with respect to the surroundings (e.g. feeling as if in a dream, or that the world is not real, external visual world is foggy or distorted)
- transient (seconds-hours) experiences of this nature are quite common in the general population
- episodes can range from hours-years, patients are often quite distressed and verbalize concern of “going crazy”

Sleep Disorders

- for more information regarding normal sleep cycles and the illnesses described, see Neurology, Sleep Disorders, N48

Overview

- adequate sleep is essential to functioning; deprivation can lead to cognitive impairment and can contribute to death
- circadian rhythms help regulate mood and cognitive performance
- neurotransmitters commonly implicated in psychiatric illnesses also regulate sleep
  - acetylcholine activity and decreased activity of monoamine neurotransmitters is associated with greater REM sleep
  - decreased adrenergic and cholinergic activity are associated with NREM sleep
- depression is associated with decreased delta (deep, slow-wave) sleep, decreased REM latency, and increased REM density
- criteria
  - must cause significant distress or impairment in functioning
  - not due to a GMC or medications/drugs (unless specified)

Management

- pharmacological treatments are illness-specific
  - non-benzodiazepines preferable (e.g. trazodone, zopiclone, quetiapine), but benzodiazepines a short term option
  - medication should not be prescribed without having first made a diagnosis and considering major psychiatric illnesses (major depression and alcohol use disorders are common etiologies)
  - sleep hygiene is a simple, effective but often underutilized method for addressing sleep disturbances. Recommendations include
    - waking up and going to bed at same time every day, including on weekends
    - avoiding long periods of wakefulness in bed
    - not using bed for non-sleep activities (reading, TV, work)
    - avoiding napping
    - discontinuing or reducing consumption of alcohol, caffeine, drugs
    - exercising at least 3-4x per week (but not in the evening, if this interferes with sleep)
Table 8. Major DSM 5 Sleep-Wake Disorders
Note: For more information regarding specific disorders, see: Neurology, Sleep Disorders, N48; Family Medicine, Sleep Disorders, FM48; and Respirology, Sleep Apnea, R31

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Uncategorized)</td>
<td>Insomnia disorder</td>
<td>Difficulty sleeping</td>
</tr>
<tr>
<td></td>
<td>Hypersomnia disorder</td>
<td>Feeling sleepy throughout the day</td>
</tr>
<tr>
<td></td>
<td>Narcolepsy</td>
<td>Recurrent attacks of irrepressible need to sleep</td>
</tr>
<tr>
<td></td>
<td>Circadian rhythm sleep-wake disorders</td>
<td>Insomnia or excessive sleepiness due to misalignment or alteration in endogenous circadian rhythm</td>
</tr>
<tr>
<td></td>
<td>Restless legs syndrome</td>
<td>Uncomfortable, frequent urge to move legs at night</td>
</tr>
<tr>
<td></td>
<td>Substance/medication-induced sleep disorder</td>
<td>Disturbance in sleep (insomnia or daytime sleepiness) caused by substance/medication intoxication or withdrawal</td>
</tr>
<tr>
<td>Breathing-related sleep disorders</td>
<td>Obstructive sleep apnea hypopnea</td>
<td>Breathing issues due to obstruction</td>
</tr>
<tr>
<td></td>
<td>Central sleep apnea</td>
<td>Breathing issues due to aberrant brain signaling</td>
</tr>
<tr>
<td></td>
<td>Sleep-related hypoventilation</td>
<td>Breathing issues due to decreased responsiveness to carbon dioxide levels</td>
</tr>
<tr>
<td>Parasomnias</td>
<td>Non-rapid eye movement sleep arousal disorders</td>
<td>Incomplete awakening from sleep, complex motor behaviour without conscious awareness; amnesia regarding episodes; includes symptoms of Sleepwalking: rising from bed and walking about, blank face, unresponsive, awakened with difficulty Sleep terrors: recurrent episodes of abrupt terror arousals from sleep, usually beginning with a panicky scream, intense fear and autonomic arousal, relative unresponsiveness to comfort during episodes Specifiers: sleep-related sexual behaviour (sexsomnia) and sleep-related eating</td>
</tr>
<tr>
<td></td>
<td>Nightmare disorder</td>
<td>Repeated extended, extremely dysphoric, often very vivid, well-remembered dreams that usually involve significant threats; rapid orientation and alertness on awakening with autonomic arousal</td>
</tr>
<tr>
<td></td>
<td>Rapid eye movement sleep behaviour disorder</td>
<td>Arousal during sleep, associated with vocalization and/or complex motor behaviours; can cause violent injuries; rapid orientation and alertness on awakening</td>
</tr>
</tbody>
</table>

Sexuality and Gender

Gender Dysphoria

Definition
- the distress that may coincide with conflict between one’s experienced/expressed gender and one’s assigned gender

Typical Presentation
- strong and persistent cross-gender identification
- desire to be rid of primary/secondary sex characteristics and to gain the primary/secondary sex characteristics of their identified gender
- repeated stated desire or insistence that one is of the opposite sex
- preference for cross-dressing, cross-gender roles in make-believe play
- intense desire to participate in the stereotypical games and pastimes of the opposite sex
- strong preference for playmates of the opposite sex
- significant distress or impairment in functioning and persistent discomfort with his or her sex or gender role

Treatment
- psychotherapy
- hormonal therapy
- sexual reassignment surgery

Paraphilic Disorders

Definition
- intense and persistent sexual interest other than sexual interest in genital stimulation or preparatory fondling with phenotypically normal, physically mature, consenting human partners
- paraphilic disorder: paraphilia that causes distress or functional impairment to the individual, or a paraphilia whose realization entails personal harm, or risk of harm to others
• subtypes: voyeuristic, exhibitionistic, frotteuristic, sexual masochism, sexual sadism, pedophilic, fetishes, transvestic, other specified paraphilic disorder, unspecified paraphilic disorder
• rarely self-referred; come to medical attention through interpersonal or legal conflict
• person usually has more than one paraphilia; 5% of paraphilias attributed to women
• typical presentation
• begins in childhood or early adolescence; increasing in complexity and stability with age
• chronic, decreases with advancing age but may increase with stress

Treatment
• anti-androgen drugs
• behaviour modification
• psychotherapy

SEXUAL DYSFUNCTION
• see Gynecology, GY33 and Urology, U30

Eating Disorders

Epidemiology
• anorexia nervosa (AN): 1% of adolescent and young adult females; onset 13-20 yr old
• bulimia nervosa (BN): 2-4% of adolescent and young adult females; onset 16-18 yr old
• F:M=10:1; mortality 5-10%

Etiology
• multifactorial: psychological, sociological, and biological associations
• individual: perfectionism, lack of control in other life areas, history of sexual abuse
• personality: obsessive-compulsive, histrionic, borderline
• familial: maintenance of weight equilibrium and control in dysfunctional family
• cultural factors: prevalent in industrialized societies, idealization of thinness in the media
• genetic factors
  ▪ AN: 6% prevalence in siblings, with one study of twin pairs finding concordance in 9 of 12 monozygotic pairs versus concordance in 1 of 14 dizygotic pairs
  ▪ BN: higher familial incidence of affective disorders than the general population

Risk Factors
• physical factors: obesity, chronic medical illness (e.g. DM)
• psychological factors: individuals who by career choice are expected to be thin, family history (mood disorders, eating disorders, substance abuse), history of sexual abuse (especially for BN), homosexual males, competitive athletes, concurrent associated mental illness (depression, OCD, anxiety disorder [especially panic and agoraphobia], substance abuse [specifically for BN])

Anorexia Nervosa

DSM-5 Diagnostic Criteria for Anorexia Nervosa
Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

A. intake and weight: restriction of energy intake relative to requirements, leading to a significantly low body weight in the context of age, sex, developmental trajectory, and physical health. Significantly low weight is defined as a weight that is less than minimally normal or, for children and adolescents, less than that minimally expected

B. fear or behaviour: intense fear of gaining weight or of becoming fat, or persistent behaviour that interferes with weight gain, even though at a significantly low weight

C. perception: disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or persistent lack of recognition of the seriousness of the current low body weight

• specifiers: partial remission, full remission, severity based on BMI (mild = BMI >17 kg/m², moderate = BMI 16-16.99 kg/m², severe = BMI 15-15.99 kg/m², extreme = BMI <15 kg/m²), type (restricting = during last 3 mo no episodes of binge-eating or purging vs. binge-eating/purging type = in last 3 mo have participated in recurrent episodes of binge-eating/purging)

Management
• psychotherapy: individual, group, family (gold standard): address food and body perception, coping mechanisms, health effects
• medications of little value
• outpatient programs and inpatient programs are available
• inpatient hospitalization for treatment of eating disorders is rarely on an acute basis (unless there is a concurrent psychiatric reason for emergent admission e.g. suicide risk)
• admit to a medical ward for hospitalization: <65% of standard body weight (<85% of standard body weight for adolescents), hypovolemia requiring intravenous fluid, heart rate <40 bpm, abnormal serum chemistry or if actively suicidal
• agree on target body weight on admission and reassure this weight will not be surpassed
• monitor for complications of AN (see Table 9)
• monitor for refeeding syndrome

Athletic Triad
• Disordered eating
• Amenorrhea
• Osteoporosis

Some patients with insulin-dependant DM may stop their insulin in order to lose weight
a potentially life-threatening metabolic response to refeeding in severely malnourished patients resulting in severe shifts in fluid and electrolyte levels
- complications include hypophosphatemia, congestive heart failure, cardiac arrhythmias, delirium, and death
- prevention: slow refeeding, gradual increase in nutrition, supplemental phosphorus, close monitoring of electrolytes and cardiac status

**Prognosis**
- early intervention much more effective (adolescent onset has much better prognosis than adult onset)
- 1 in 10 adolescents continue to have anorexia nervosa as adults
- with treatment, 70% resume a weight of at least 85% of expected levels and about 50% resume normal menstrual function
- eating peculiarities and associated psychiatric symptoms are common and persistent
- long-term mortality: 10-20% of patients hospitalized will die in next 10-30 yr (secondary to severe and chronic starvation, metabolic or cardiac catastrophes, with a significant proportion committing suicide)

### Bulimia Nervosa

**DSM-5 Diagnostic Criteria for Bulimia Nervosa**

Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2013. American Psychiatric Association

- **A.** recurrent episodes of binge-eating; an episode of binge-eating is characterized by both of the following
  - eating, in a discrete period of time, an amount of food that is definitely larger than what most individuals would eat during a similar period of time and under similar circumstances
  - a sense of lack of control over eating during the episode
- **B.** recurrent inappropriate compensatory behaviour in order to prevent weight gain, such as self-induced vomiting, misuse of laxatives, diuretics, enemas, or other medications, fasting, or excessive exercise
- **C.** the binge-eating and inappropriate compensatory behaviours both occur, on average, at least once a week for 3 mo
- **D.** self-evaluation is unduly influenced by body shape and weight
- **E.** the disturbance does not occur exclusively during episodes of AN
  - **specifiers:** partial remission, full remission, severity (mild = 1-3 inappropriate compensatory behaviours/wk, moderate = 4-7 inappropriate compensatory behaviours/wk, severe = 8-13 inappropriate compensatory behaviours/wk, extreme = 14+ inappropriate compensatory behaviours/wk)

**Associated Features**
- fatigue and muscle weakness due to repetitive vomiting and fluid/electrolyte imbalance
- tooth decay
- swollen appearance around angle of jaw and puffiness of eye sockets due to fluid retention
- reddened knuckles, Russell's sign (knuckle callus from self-induced vomiting)
- trouble concentrating
- weight fluctuation over time

**Management**
- admission for significant electrolyte abnormalities
- biological: treatment of starvation effects, SSRIs (fluoxetine most evidence) as adjunct
- psychological: develop trusting relationship with therapist to explore personal etiology and triggers, CBT, family therapy, recognition of health risks
- social: challenge destructive societal views of women, use of hospital environment to provide external patterning for normative eating behaviour

**Prognosis**
- relapsing/remitting disease
- good prognostic factors: onset before age 15, achieving a healthy weight within 2 yr of treatment
- poor prognostic factors: later age of onset, previous hospitalizations, individual and familial disturbance
- 60% good treatment outcome, 30% intermediate outcome, 10% poor outcome
### Binge-Eating Disorder

**Definition**
- recurrent episodes of binge-eating (as defined by criteria A of BN) that are associated with eating much more rapidly than normal, eating until feeling uncomfortably full, eating large amounts when not physically hungry, eating alone because embarrassed by how much one is eating, feeling disgusted with oneself/depressed/very guilty afterwards at least once/wk x 3 mo
- not associated with any compensatory behaviours
- dieting usually follows binge-eating (vs. BN where dysfunctional dieting typically precedes binge-eating)
- associated with health consequences (e.g. increased risk of weight gain, obesity)

**Epidemiology**
- F:M = 2:1
- begins in adolescence or young-adulthood

**Treatment**
- hallmark is CBT

### Avoidant/Restrictive Food Intake Disorder

**Definition**
- eating/feeding disturbance to the point that there is persistent failure to meet appropriate nutritional and/or energy needs such that individual experiences significant weight loss/growth failure, have nutritional deficiencies, may become dependent on enteral feeding/oral nutritional supplementation, has a marked interference with psychosocial functioning
  - does not occur during an episode of AN or BN
  - no evidence of distress in the way in which one's body weight or shape is experienced

**Risk Factors**
- temperament (e.g. anxiety disorders), environment (e.g. familial anxiety), genetic (e.g. history of GI conditions)
- begins in infancy and can persist into adulthood

**Treatment**
- watchful waiting
- behaviour modification
- psychotherapy

### Table 9. Physiologic Complications of Eating Disorders

<table>
<thead>
<tr>
<th>System</th>
<th>Starvation/Restriction</th>
<th>Binge-Purge</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Low BP, low HR, significant orthostatic changes ± syncopal episodes, low temperature, vitamin deficiencies</td>
<td>Russell's sign (knuckle callus) Parotid gland enlargement Perioral skin irritation Periocular and palatal petechiae Loss of dental enamel and caries Aspiration pneumonia Metabolic alkalosis secondary to hypokalemia and loss of acid</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Primary or secondary amenorrhea, decreased T3/T4</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Grand mal seizure (decreased Ca++, Mg++, PO43-)</td>
<td></td>
</tr>
<tr>
<td>Cutaneous</td>
<td>Dry skin, lanugo hair, hair loss or thinning, brittle nails, yellow skin from high carotene</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>Constipation, GERD, delayed gastric emptying</td>
<td>Acute gastric dilation/rupture, pancreatitis, GERD, hematemesis secondary to Mallory-Weiss tear</td>
</tr>
<tr>
<td>CVS</td>
<td>Anrhymias, CHF</td>
<td>Anrhymias, cardiomyopathy (from use of ipecac), sudden cardiac death (decreased K+)</td>
</tr>
<tr>
<td>MSK</td>
<td>Osteoporosis secondary to hypogonadism</td>
<td>Muscle wasting</td>
</tr>
<tr>
<td>Renal</td>
<td>Pre-renal failure (hypovolemia), renal calculi</td>
<td>Renal failure (electrolyte disturbances)</td>
</tr>
<tr>
<td>Extremities</td>
<td>Pedal edema (decreased albumin)</td>
<td>Pedal edema (decreased albumin)</td>
</tr>
<tr>
<td>Lab Values</td>
<td>Starvation: decreased RBCs, decreased WBCs, decreased LH, decreased FSH, decreased estrogen, decreased testosterone, increased growth hormone, increased cholesterol Dehydration: increased BUN</td>
<td>Vomiting: decreased Na+, decreased K+, decreased Cl-, decreased H+, increased amylase; hypokalemia with metabolic alkalosis Laxatives: decreased Na+, decreased K+, decreased Cl-, increased H+; metabolic acidosis</td>
</tr>
</tbody>
</table>
Personality Disorders

- an evolving personality disorder literature describes that personality is better understood using a trait-based dimensional approach (e.g. 5 major traits such as extraversion, agreeableness, conscientiousness, neuroticism, and openness to experiences rated on a continuum of dysfunctional effects) rather than discrete categories; however, the discrete categories still remain in the current DSM and will be referenced here

General Information
- an enduring pattern of inner experience and behaviour that deviates markedly from the expectations of the individual’s culture; manifested in two or more of: cognition, affect, interpersonal functioning, impulse control
- inflexible and pervasive across a range of situations
- pattern is stable and well established by adolescence or early adulthood (vs. a sudden onset)
- associated with many complications, such as depression, suicide, violence, brief psychotic episodes, multiple drug use, and treatment resistance
- relationship building and establishing boundaries are important; focus should be placed on validating, finding things to be truly empathetic about, and speaking to strengths
- mainstay of treatment is psychotherapy with the addition of pharmacotherapy to treat associated axis I disorders (i.e. depression, anxiety, substance abuse)

Classification
- personality disorders are divided into three clusters (A, B, and C), with shared features among disorders within each

Table 10. Description and Diagnosis of Personality Disorders

<table>
<thead>
<tr>
<th>Cluster A “Mad” Personality Disorders</th>
<th>Cluster B “Odd” Personality Disorders</th>
<th>Cluster C “Deviant” Personality Disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paranoid Personality Disorder (0.5%-3%)</td>
<td>Schizotypal Personality Disorder (3.5-6%)</td>
<td>Schizoid Personality Disorder</td>
</tr>
<tr>
<td>Pervasive distrust and suspiciousness of others, interpret motives as malevolent</td>
<td>Pattern of eccentric behaviours, peculiar thought patterns</td>
<td>Neither desires nor enjoys close relationships including being a part of a family; prefers to be alone</td>
</tr>
<tr>
<td>Blame problems on others and seem angry and hostile</td>
<td>Diagnosis requires 5+ of: ME PECULIAR</td>
<td>Lifelong pattern of social withdrawal</td>
</tr>
<tr>
<td>Diagnosis requires 4+ of: SUSPECT</td>
<td>1. Magical thinking</td>
<td>Seen as eccentric and reclusive with restricted affect</td>
</tr>
<tr>
<td>1. Suspicious that others are exploiting or deceiving them</td>
<td>2. Experiences unusual perceptions (including body illusions)</td>
<td>Diagnosis requires 4 of: DISTANT</td>
</tr>
<tr>
<td>2. Unforgiving (bears grudges)</td>
<td>3. Paranoid ideation</td>
<td>1. Detached/flat affect, emotionally cold</td>
</tr>
<tr>
<td>3. Spousal infidelity suspected without justification</td>
<td>4. Eccentric behaviour or appearance</td>
<td>2. Indifferent to praise or criticism</td>
</tr>
<tr>
<td>4. Perceive attacks on character, counterattacks quickly</td>
<td>5. Constricted or inappropriate affect</td>
<td>3. Sexual experiences of little interest</td>
</tr>
<tr>
<td>5. Enemies or friends? Preoccupied with acquaintance trustworthiness</td>
<td>6. Unusual thinking/speech (e.g. vague, stereotyped)</td>
<td>4. Tasks done solitarily</td>
</tr>
<tr>
<td>6. Confiding in others is feared</td>
<td>7. Lacks close friends</td>
<td>5. Absence of close friends (other than first-degree relatives)</td>
</tr>
<tr>
<td></td>
<td>9. Anxiety in social situations</td>
<td>7. Takes pleasure in few (if any) activities</td>
</tr>
</tbody>
</table>
### Cluster B “Bad” Personality Disorders

- Patients seem dramatic, emotional, inconsistent
- Familial association with mood disorders
- Common defense mechanisms: denial, acting out, regression (histrionic PD), splitting (borderline PD), projective identification, idealization/devaluation

#### Borderline Personality Disorder (2-4%)

- Unstable moods and behaviour, feel alone in the world, problems with self-image. History of repeated suicide attempts, self-harm behaviours. Inpatients commonly report history of sexual abuse. Tends to fizzle out as patients age. DBT is the principal treatment (see Psychotherapy, PS43).
- **10% suicide rate**

**Diagnosis requires 5+ of:**

<table>
<thead>
<tr>
<th>IMPULSIVE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Impulsive (min. 2 self-damaging ways, e.g. sex/drugs/spending)</td>
</tr>
<tr>
<td>2. Mood/affect instability</td>
</tr>
<tr>
<td>3. Paranoia or dissociation under stress</td>
</tr>
<tr>
<td>4. Unstable self-image</td>
</tr>
<tr>
<td>5. Labile intense relationships</td>
</tr>
<tr>
<td>6. Suicidal gestures / self-harm</td>
</tr>
<tr>
<td>7. Inappropriate anger</td>
</tr>
<tr>
<td>8. Avoiding abandonment (real or imagined, frantic efforts to)</td>
</tr>
<tr>
<td>9. Emptiness (feelings of)</td>
</tr>
</tbody>
</table>

#### Narcissistic Personality Disorder (2%)

- Sense of superiority, needs constant admiration, lacks empathy, but with fragile sense of self.
- Consider themselves “special” and will exploit others for personal gain

**Diagnosis requires 5+ of:**

<table>
<thead>
<tr>
<th>GRANDIOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Grandiose</td>
</tr>
<tr>
<td>2. Requires excessive admiration</td>
</tr>
<tr>
<td>3. Arrogant</td>
</tr>
<tr>
<td>4. Needs to be special (and associate with other specials)</td>
</tr>
<tr>
<td>5. Dreams of success, power, beauty, love</td>
</tr>
<tr>
<td>6. Interpersonally exploitative</td>
</tr>
<tr>
<td>7. Others (lacks empathy, unable to recognize feelings/needs of)</td>
</tr>
<tr>
<td>8. Sense of entitlement</td>
</tr>
<tr>
<td>9. Envious (or believes others are envious)</td>
</tr>
</tbody>
</table>

#### Antisocial Personality Disorder (M: 3%, F: 1%)

- Lack of remorse for actions, manipulative and deceitful, often violate the law. May appear charming on first impression. Pattern of disregard for others and violation of others’ rights must be present before age 15; however, for the diagnosis of ASPD patients must be at least 18. Strong association with Conduct Disorder, history of trauma/abuse common (see Child Psychiatry).

**Diagnosis requires 5+ of:**

<table>
<thead>
<tr>
<th>CORRUPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Cannot conform to law</td>
</tr>
<tr>
<td>2. Obligations ignored (irresponsible)</td>
</tr>
<tr>
<td>3. Reckless disregard for safety</td>
</tr>
<tr>
<td>4. Ransomless</td>
</tr>
<tr>
<td>5. Underhanded (deceitful)</td>
</tr>
<tr>
<td>6. Planning insufficient (impulsive)</td>
</tr>
<tr>
<td>7. Temper (irritable and aggressive)</td>
</tr>
</tbody>
</table>

#### Histrionic Personality Disorder (1.3-3%)

- Attention-seeking behaviour and excessively emotional. Are dramatic, flamboyant, and extroverted. Cannot form meaningful relationships. Often sexually inappropriate

**Diagnosis requires 5+ of:**

<table>
<thead>
<tr>
<th>ACTRESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Appearance used to attract attention</td>
</tr>
<tr>
<td>2. Center of attention (else uncomfortable)</td>
</tr>
<tr>
<td>3. Theatrical</td>
</tr>
<tr>
<td>4. Relationships (believed to be more intimate than they are)</td>
</tr>
<tr>
<td>5. Easily influenced</td>
</tr>
<tr>
<td>6. Seductive behaviour</td>
</tr>
<tr>
<td>7. Shallow expression of emotions (which rapidly shift)</td>
</tr>
<tr>
<td>8. Speech (impressionistic and vague)</td>
</tr>
</tbody>
</table>

#### Cluster C “Sad”

- Patients seem anxious, fearful
- Familial association with anxiety disorder
- Common defense mechanisms: isolation, avoidance, hypochondriasis

#### Avoidant Personality Disorder (0.5-1.6%)

- Timid and socially awkward with a pervasive sense of inadequacy and fear of criticism. Fear of embarrassing or humiliating themselves in social situations so remain withdrawn and socially inhibited

**Diagnosis requires 4+ of:**

<table>
<thead>
<tr>
<th>CRINGES</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Criticism or rejection preoccupies thoughts in social situations</td>
</tr>
<tr>
<td>2. Restrained in relationships due to fear of being harmed</td>
</tr>
<tr>
<td>3. Inhibited in new relationships due to fear of inadequacy</td>
</tr>
<tr>
<td>4. Needs to be sure of being liked before engaging socially</td>
</tr>
<tr>
<td>5. Gets around occupational activities requiring interpersonal contact</td>
</tr>
<tr>
<td>6. Embarrassment prevents new activity or taking risks</td>
</tr>
<tr>
<td>7. Self-viewed as unappealing or inferior</td>
</tr>
</tbody>
</table>

#### Obsessive-Compulsive Personality Disorder (3-10%)

- Preoccupation with orderliness, perfectionism, and mental and interpersonal control. Is inflexible, closed-off, and inefficient

**Diagnosis requires 4+ of:**

<table>
<thead>
<tr>
<th>SCRIMPER</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Stubborn</td>
</tr>
<tr>
<td>2. Cannot discard worthless objects</td>
</tr>
<tr>
<td>3. Rule/detox obsessed (to point of activity lost)</td>
</tr>
<tr>
<td>4. Inflexible in matters of morality, ethics, values</td>
</tr>
<tr>
<td>5. Miserly</td>
</tr>
<tr>
<td>6. Perfectionistic</td>
</tr>
<tr>
<td>7. Excludes leisure due to devotion to work</td>
</tr>
<tr>
<td>8. Reluctant to delegate to others</td>
</tr>
</tbody>
</table>

#### Dependent Personality Disorder (1.5-6.7%)

- Pervasive and excessive need to be taken care of, excessive fear of separation, clinging and submissive behaviours. Difficulty making everyday decisions. Useful to set regulated treatment schedule (regular, brief visits) and being firm about in between issues. Encourage patient to do more for themselves, engage in own problem-solving

**Diagnosis requires 5+ of:**

<table>
<thead>
<tr>
<th>RELIANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Reassurance required for everyday decisions</td>
</tr>
<tr>
<td>2. Expressing disagreement difficult</td>
</tr>
<tr>
<td>3. Life responsibilities assumed by others</td>
</tr>
<tr>
<td>4. Initiating projects difficult (because no confidence)</td>
</tr>
<tr>
<td>5. Alone (feels helpless and uncomfortable when alone)</td>
</tr>
<tr>
<td>6. Nurturance (goes to excessive lengths to obtain)</td>
</tr>
<tr>
<td>7. Companionship sought urgently</td>
</tr>
<tr>
<td>8. Exaggerated fears of being left to care for self</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Table 10. Description and Diagnosis of Personality Disorders (continued)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cluster B “Bad” Personality Disorders</strong></td>
</tr>
<tr>
<td><strong>Borderline Personality Disorder (2-4%)</strong></td>
</tr>
<tr>
<td><strong>Narcissistic Personality Disorder (2%)</strong></td>
</tr>
<tr>
<td><strong>Antisocial Personality Disorder (M: 3%, F: 1%)</strong></td>
</tr>
<tr>
<td><strong>Histrionic Personality Disorder (1.3-3%)</strong></td>
</tr>
<tr>
<td><strong>Cluster C “Sad”</strong></td>
</tr>
<tr>
<td><strong>Avoidant Personality Disorder (0.5-1.6%)</strong></td>
</tr>
<tr>
<td><strong>Obsessive-Compulsive Personality Disorder (3-10%)</strong></td>
</tr>
<tr>
<td><strong>Dependent Personality Disorder (1.5-6.7%)</strong></td>
</tr>
</tbody>
</table>

---
Table 11. Key Differences Among Schizoid, Schizotypal, and Schizophrenia

<table>
<thead>
<tr>
<th></th>
<th>Schizoid</th>
<th>Schizotypal</th>
<th>Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thought Form</td>
<td>Organized</td>
<td>Organized, but vague and</td>
<td>Disorganized, tangential,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>circumstantial</td>
<td>loosening of associations</td>
</tr>
<tr>
<td>Thought Content</td>
<td>No psychosis</td>
<td>No psychosis, may have ideas</td>
<td>Psychosis, hallucinations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>of reference, paranoid</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>ideation, odd beliefs and</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>magical thinking</td>
<td></td>
</tr>
<tr>
<td>Relationships</td>
<td>Solitary, NO desire for social relationships</td>
<td>Lacks close relationships, INTERESTED in relationships but socially inept</td>
<td>Socially marginalized, but not by choice</td>
</tr>
</tbody>
</table>

Child Psychiatry

Developmental Concepts

- **temperament**: innate psycho-physiological and behavioural characteristics of a child (e.g. emotionality, activity, and sociability); spectrum from “difficult” to “slow-to-warm-up” to “easy temperament”
- **parental fit**: the congruence between parenting style (authoritative, authoritarian, permissive) and child’s temperament
- **attachment**: special relationship between child and primary caretaker(s); develops during first year, best predictor of a child’s attachment style is their parent’s attachment style
- **separation anxiety** (normal between 10-18 mo): separation from attachment figure results in distress

Table 12. Attachment Models

<table>
<thead>
<tr>
<th>Parent/Caregiver</th>
<th>Attachment Type</th>
<th>Features in Child</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loving, consistently available, sensitive, and receptive</td>
<td>Secure</td>
<td>Freely explore and engage strangers well (as long as mother in close proximity), upset with caregiver departure, happy with return</td>
</tr>
<tr>
<td>Rejecting, unavailable psychologically, insensitive responses</td>
<td>Insecure (avoidant)</td>
<td>Ignore caregiver, show little emotion with arrival or departure, little exploration</td>
</tr>
<tr>
<td>Inconsistent, insensitive responses, role reversal</td>
<td>Insecure (ambivalent/resistant)</td>
<td>Clingy but inconsolable, often display anger or helplessness, little exploration</td>
</tr>
<tr>
<td>Frightening, dissociated, sexualized, or atypical Often history of trauma or loss</td>
<td>Disorganized</td>
<td>Simultaneous approach/avoidance and stress related straining behaviour</td>
</tr>
</tbody>
</table>

Mood Disorders

MAJOR DEPRESSIVE DISORDER

Epidemiology

- pre-pubertal 1-2% (no gender differences); post-pubertal 4-18% (F:M = 2:1)

Clinical Presentation

- see Mood Disorders, PS9
- only difference in diagnostic criteria is that irritable mood may replace depressed mood
- physical factors: insomnia (children), hypersomnia (adolescents), somatic complaints, substance abuse, decreased hygiene
- psychological factors: irritability, boredom, anhedonia, low self-esteem, deterioration in academic performance, social withdrawal, lack of motivation, listlessness
- comorbid diagnoses of anxiety, ADHD, ODD, conduct disorder, and eating disorders

Treatment

- majority never seek treatment
- individual (CBT, IPT)/family therapy and education, modified school program
- SSRIs (strongest evidence for fluoxetine 10-40mg/d)
- close follow-up on adolescents starting SSRIs to monitor for increased suicidal ideation or behaviour
- in severe depression, best evidence for combined pharmacotherapy and psychotherapy
- ECT: only in adolescents who have severe illness, psychotic features, catatonic features, persistently suicidal
- light therapy, self-help books
**Prognosis**
- prolonged episodes, up to 1-2 yr
- adolescent onset predicts chronic mood disorder; up to 2/3 will have another depressive episode within 5 yr
- complications
- negative impact on family and peer relationships
- school failure
- significantly increased risk of suicide attempt (10%) or completion (however, suicide risk low for pre-pubertal children)
- substance abuse

**DISRUPTIVE MOOD DYSREGULATION DISORDER**

**Clinical Presentation**
- severe, developmentally inappropriate, recurrent verbal or behavioural temper outbursts at least 3 times per wk
- mood is predominantly irritable or angry in between outbursts, as observable by others
- these symptoms occur before 10 y, have been occurring for 12 mo, with no more than 3 consecutive mo free from symptoms
- high rates of comorbidities; ADHD, ODD, anxiety disorders, depressive disorders

**BIPOLAR DISORDER**

**Clinical Presentation**
- see *Bipolar Disorder, PS13*
- mixed presentation and psychotic symptoms (hallucinations and delusions) more common in adolescent population than adult population
- unipolar depression may be an early sign of adult bipolar disorder
- ~30% of psychotic depressed adolescents receive a bipolar diagnosis within 2 yr of presentation
- associated with rapid onset of depression, psychomotor retardation, mood-congruent psychosis, affective illness in family, pharmacologically-induced mania

**Treatment**
- Pharmacotherapy: mood stabilizers and/or antipsychotics
- Psychotherapy: CBT, Family Focused Therapy

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**Anxiety Disorders**

- lifetime prevalence 10-20%; F:M = 2:1

**Clinical Presentation**
- children and adolescents rarely vocalize their anxiety but instead demonstrate it through their behaviour
- school problems, recurrent physical symptoms (abdominal pain, headaches) especially in mornings, social and relationship problems, social withdrawal and isolation, family conflict, difficulty with sleep initiation, irritability and mood symptoms, alcohol and drug use in adolescent

**Differential Diagnosis**
- clinical judgment important to differentiate developmentally normal from pathological anxiety
- for school avoidance, differentiate fear of general performance, humiliation, worry about separation and rule out bullying and school refusal due to learning disorder
- depressive disorders, ODD, truancy

**Course and Prognosis**
- better prognosis with later age of onset, lower co-morbidities, early initiation of treatment, ability to maintain school attendance and peer relationships, absence of social anxiety disorder
- with treatment up to 80% of children will not meet criteria for their anxiety disorder at 3 year follow-up but up to 30% will meet criteria for another psychiatric disorder

**Treatment**
- similar principles for most childhood anxiety disorders due to overlapping symptomatology and frequent comorbidity
- family psychotherapy, predictive and supportive environment
- CBT: child and parental education, relaxation techniques (e.g. deep breathing), exposure/desensitization, recognizing and correcting anxious thoughts
- pharmacotherapy: SSRIs (e.g. fluoxetine, paroxetine), benzodiazepines (alprazolam, clonazepam have evidence – use with caution due to addictive and abuse potential as well as disinhibiting effect, especially in neurodevelopmental delay)
  - fluvoxamine and sertraline also have good evidence, particularly for OCD
SEPARATION ANXIETY DISORDER
- excessive and developmentally inappropriate anxiety on real, threatened or imagined separation from primary caregiver or home with physical or emotional distress for at least 4 wk
- school refusal (75%)
- persistent worry, refusal to sleep alone, clinging, nightmares involving separation, somatic symptoms
- comorbid major depression common (2/3)
- worry about something happening to parent or themselves if separated

SOCIAL PHOBIA (SOCIAL ANXIETY DISORDER)
- situations in which the child feels they are exposed to scrutiny by others can provoke anxiety and become feared or avoided
- must distinguish between shy child, child with issues functioning socially (e.g. autism), and child with social anxiety
  - diagnosis only if anxiety interferes significantly with daily routine, social life, academic functioning or if markedly distressed. Must occur in settings with peers, not just adults
  - features: temper tantrums, freezing, clinging behaviour, mutism, excessively timid, stays on periphery, refuses to be involved in group play
  - significant implication for future quality of life if untreated; lower levels of satisfaction in leisure activities, higher rates of school dropout, poor workplace performance, increased rates of remaining single

SELECTIVE MUTISM
- consistent failure to speak in specific social situations in which there is an expectation for speaking despite speaking in other situations
- the disturbance interferes with educational or occupational achievement or with social communication

GENERALIZED ANXIETY DISORDER
- diagnostic criteria same as adults (see Generalized Anxiety Disorder, PS16)
  - note: only 1 item is required in children for Criteria C
- often redo tasks, show dissatisfaction with their work, and tend to be perfectionistic
- often fearful in multiple settings and expect more negative outcomes when faced with academic or social challenges, and require reassurance and support to take on new tasks

SPECIFIC PHOBIA
- common phobias in childhood include a fear of heights, small animals, doctors, dentists, darkness, loud noises, thunder and lightning

Neurodevelopmental Disorders

Autism Spectrum Disorder

Diagnosis
- persistent deficits in social communication and interaction, manifested in three areas
  - social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation, to reduced sharing of interests, emotions, or affect, to failure to initiate or respond to social interactions
  - nonverbal communicative behaviours, ranging, for example, from poorly integrated verbal and nonverbal communication, to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication
  - developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behaviour to suit various social contexts, to difficulties in sharing imaginative play or in making friends, to absence of interest in peers
- restricted, repetitive patterns of behaviour, interests, or activities. Two or more of: stereotyped or repetitive motor movements, insistence on sameness, highly restricted fixed interests, hyper-/ hypo-reactivity to sensory input
- symptoms must be present in early developmental period
- symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
- not better explained by intellectual disability or global developmental delay
- specifiers
  - current severity: requiring very substantial support, requiring substantial support, requiring support
  - with or without accompanying language impairment
  - with or without accompanying intellectual impairment
  - associated with known medical or genetic condition or environmental factors (i.e. Rett’s disorder)

Differential Diagnosis
- developmental disability, childhood schizophrenia, social phobia, OCD, communication disorder, non-verbal learning disorder, ADHD, abuse, hearing or visual impairment, seizure disorder, motor impairment

Management
- hearing and vision test to rule out impairment
- psychological testing to assess intellectual functioning and learning
- chromosomal analysis to rule out abnormalities (e.g. Trisomy 21, Fragile X syndrome)
- rule out psychotic disorders, social problems, depression, anxiety, abuse

Treatment
- team-based: school, psychologist, occupational therapist, physiotherapist, speech and language therapy, pediatrics, psychiatry
- psychosocial: family education and support, school programming, behaviour management, social skills training
- treat concomitant disorders such as ADHD, tics, OCD, anxiety, depression, and seizure disorder
- pharmacotherapy: atypical antipsychotics (for irritability, aggression, agitation, self-mutilation, tics), SSRIs (for anxiety, depression), stimulants (for associated inattention and hyperactivity)

Prognosis
- variable, but improves with early intervention
- better if IQ >60 and able to communicate

Attention Deficit Hyperactivity Disorder
- prevalence: 5-12% of school-aged children; M:F = 4:1, although girls may be under-diagnosed
- girls tend to have inattentive/distractible symptoms; boys have impulsive/hyperactive symptoms

Etiology
- genetic: 75% heritability, dopamine candidate genes DAT1, DRD4
- neurobiology: decreased catecholamine transmission, low prefrontal cortex (PFC) activity, increased beta activity on EEG
- cognitive: developmental disability, poor inhibitory control and other errors of executive function

Diagnosis
- differential: learning disorders, hearing/visual defects, thyroid, atopic conditions, congenital problems (fetal alcohol syndrome, Fragile X), lead poisoning, history of head injury, traumatic life events (abuse)
- diagnosis (3 subtypes)
  - combined type: 6 or more symptoms of inattention and 6 or more symptoms of hyperactivity-impulsivity
  - predominantly inattentive type: 6 or more symptoms of inattention
  - predominantly hyperactive-impulsive type: 6 or more symptoms of hyperactivity-impulsivity
- for older adolescents (>17 yr) or adults, 5 symptoms required
- symptoms persist for >6 mo
- onset before age 12
- symptoms present in at least two settings (i.e. home, school, work)
- interferes with academic, family, and social functioning
- does not occur exclusively during the course of another psychiatric disorder

Observe child for “ATTENTION” features
- Annoying
- Temperamental
- Energetic
- Noisy
- Task incompletion
- Inattentive
- Oppositional
- Negativism
Table 13. Core Symptoms of ADHD (DSM-5)

<table>
<thead>
<tr>
<th>Inattention</th>
<th>Hyperactivity</th>
<th>Impulsivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Careless mistakes</td>
<td>Fidgets, squirms in seat</td>
<td>Blurs out answers before questions completed</td>
</tr>
<tr>
<td>Cannot sustain attention in tasks or play</td>
<td>Leaves seat when expected to remain seated</td>
<td>Difficulty awaiting turn</td>
</tr>
<tr>
<td>Does not listen when spoken to directly</td>
<td>Runs and climbs excessively</td>
<td>Interrupts/intrudes on others</td>
</tr>
<tr>
<td>Fails to complete tasks</td>
<td>“On the go”, driven by a motor</td>
<td></td>
</tr>
<tr>
<td>Disorganized</td>
<td>Cannot play quietly</td>
<td></td>
</tr>
<tr>
<td>Avoids, dislikes tasks that require sustained mental effort</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Loses things necessary for tasks or activities</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Distractible</td>
<td>Talks excessively</td>
<td></td>
</tr>
<tr>
<td>Forgetful</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Features
- difficult to differentiate from highly variable normative behaviour before age 4
- often identified upon school entry
- rule out developmental delay, sensory impairments, genetic syndromes, encephalopathies or toxins (alcohol, lead)
- risk of substance abuse, depression, anxiety, academic failure, poor social skills, risk of comorbid CD and/or ODD, risk of adult ASPD
- associated with family history of ADHD, difficult temperamental characteristics

Treatment
- non-pharmacological: parent management, anger control strategies, positive reinforcement, social skills training, individual/family therapy, behaviour therapy, tutors, classroom intervention, exercise routines, extracurricular activities, omega-3 fatty acids
- pharmacological
  - first line: stimulants (methylphenidate, amphetamine salts)
  - second line: atomoxetine
  - third line/adjunct: nonstimulants (a-agonists; clonidine, guanfacine, NDRI; bupropion)
- for comorbid symptoms: antidepressants, antipsychotics

Prognosis
- 70-80% continue into adolescence, but hyperactive symptoms usually abate
- 65% continue into adulthood; secondary personality disorders and compensatory anxiety disorders are identifiable

Disruptive, Impulse Control, and Conduct Disorder

Oppositional Defiant Disorder

- prevalence: 2-16%, M=F after puberty

Diagnosis
- pattern of negativistic/hostile and defiant behaviour for ≥6 mo with ≥4 of
  - angry/irritable mood: easily loses temper, touchy or easily annoyed, often angry and resentful
  - argumentative/defiant: argues with adults/authority figure, defies requests/rules, deliberately annoys, blames others for their own mistakes or misbehaviour
  - vindictiveness: spiteful or vindictive twice in past 6 mo
- behaviour causes significant impairment in social, academic, or occupational functioning
- behaviours do not occur exclusively during the course of a psychotic or mood disorder
- criteria not met for conduct disorder (CD); if 18 yr or older, criteria not met for ASPD
- may progress to CD, differentiated by an absence of destructive or physically aggressive behaviour
- features that typically differentiate ODD from transient developmental stage: onset <8 yr, chronic duration (>6 mo), frequent intrusive behaviour
- impact of ODD: poor school performance, few friends, strained parent/child relationships, risk of later mood disorders

Treatment
- parent: management training, psychoeducation and family therapy to reduce punitive parenting and parent-child conflict
- behavioural therapy: to teach, practice and reinforce prosocial behaviour
- social: school/day-care interventions
- pharmacotherapy for comorbid disorders
Conduct Disorder

- prevalence: 1.5-3.4% (M:F = 4-12:1)

Etiology
- parental/familial factors: parental psychopathology (e.g. ASPD, substance abuse), child-rearing practices (e.g. child abuse, discipline), low socioeconomic status (SES), family violence
- child factors: difficult temperament, ODD, learning problems, neurobiology

Diagnosis
- differential: ADHD, depression, head injury, substance abuse
- diagnosis: use multiple sources (Achenbach Child Behavioural Checklist, Teacher's Report Form)
  - pattern of behaviour that violates rights of others and age appropriate social norms with ≥3 criteria noted in past 12 mo and ≥1 in past 6 mo
  - aggression to people and animals: bullying, initiating physical fights, use of weapons, forced sex, cruel to people, cruel to animals, stolen while confronting a person (e.g. armed robbery)
  - destruction of property: fire setting with intent to damage, deliberately destroying others’ property
  - deceitfulness or theft: breaking and entering, conning others, stealing nontrivial items without confrontation
  - violation of rules: out all night before age 13, often truant from school before age 13, runaway ≥2 times at least overnight or for long periods of time
- disturbance causes clinically significant impairment in social, academic, or occupational functioning
- if individual is 18 yr or older, criteria not met for ASPD
- diagnostic types
  - childhood onset: at least one criterion prior to age 10
  - poor prognosis: associated with ODD, aggressiveness, impulsiveness
  - adolescent onset: absence of any criteria until age 10
  - better prognosis; least aggressive, gang-related delinquency
  - mild, moderate, severe

Treatment
- early intervention necessary and more effective; long-term follow-up required
- psychosocial: parent management training, anger replacement training, CBT, family therapy, education/employment programs, social skills training,
- pharmacotherapy: for comorbid disorders

Prognosis
- poor prognostic indicators include early-age onset, high frequency, variety of behaviours, pervasiveness (i.e. in home, school, community), comorbid ADHD, early sexual activity, substance abuse
- 50% of CD children become adult ASPD

Intermittent Explosive Disorder

Diagnosis
- recurrent behavioural outbursts representing a failure to control aggressive impulses in children > 6 yr, manifested as either
  - verbal or physical aggression that does not damage others or property, occurring 2+ times per wk for 3 mo
  - 3 outbursts involving physical damage to another person, animal or piece of property in the last 12 mo
- outbursts are out of proportion to triggers or provocation, are not premeditated, and not for primary gain
- outbursts cause clinically significant impairment in social, academic, or occupational functioning

See Pediatrics
- Child Abuse, P14
- Chronic Abdominal Pain, P40
- Developmental Delay, P22
- Intellectual Disability, P23
- Learning Disabilities, P24
- Sleep Disturbances, P13

See Neurology
- Tic Disorders, N34
- Tourette’s Syndrome, N35
Psychotherapy

- treatment in which a person with mental or physical difficulties aims to achieve symptomatic relief through talks with another person
- psychotherapy is delivered by a specially trained social worker, nurse, psychologist, psychiatrist, counselor or general practitioner
- various types of therapy exist because of diverse theories of human psychology and mental illness etiology

Common Factors of Psychotherapy

- good evidence that effective psychotherapy creates observable changes in brain circuitry and connectivity, similar to those observed with successful pharmacologic and other treatment modalities
- studies suggest that up to 30-70% of therapy outcome is due to common factors with only 10-40% from specific factors
- common factors: warmth (unconditional positive regard), accurate empathy, genuineness, goodness of fit

Table 14. Summary of Psychotherapeutic Modalities

<table>
<thead>
<tr>
<th>Type</th>
<th>Indications</th>
<th>Approach, Technique and Theory</th>
<th>Ideal Candidates</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychoanalytic/psychodynamic</td>
<td>Psychoneuroses; anxiety, obsessional thinking, compulsive or conversion disorders, sexual dysfunction, depressive states</td>
<td>Theory: Exploration of meaning of early experiences and how they affect emotions and patterns of behaviour. Recollection (remembering), repetition (relying on the analyst), working through (gaining insight) Techniques: free association, dream interpretation, transference analysis</td>
<td>Psychologically minded, highly motivated, wish to understand selves and not just relieve symptoms Able to withstand difficult emotions without fleeing or self-destructive acts High level of function</td>
<td>Time intensive: 12-20 wk for 3-7 yr Psychodynamically oriented therapy: 2-3 times/wk for fewer years</td>
</tr>
<tr>
<td>Supportive</td>
<td>Adjustment disorders, psychosomatic disorders, severe psychotic or personality disorders</td>
<td>Ameliorate symptoms through behavioural or environmental restructuring to aid adaptation and facilitate coping Help patients feel safe, secure and encouraged</td>
<td>Individuals in crisis or with severe symptoms in acute or chronic settings Low insight, low motivation, &quot;weak&quot; ego systems Variable (single session to years, though often short-intermittent)</td>
<td>12-20 wk</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>Mood disorders, bulimia nervosa</td>
<td>Focuses on how interpersonal relationships impact symptoms 4 key problem areas addressed: grief and loss, role transitions, conflict, interpersonal deficits Break the interpersonal cycle: depression, self-esteem, social withdrawal</td>
<td>Individuals with depression or bipolar disorder with some insight and difficult social functioning Absence of severe psychotic process, personality disorder or comorbid substance abuse 12-20 wk</td>
<td>Usually short term (weeks-months)</td>
</tr>
<tr>
<td>Behavioural</td>
<td>Most mental health disorders benefit from specific application of behavioural therapy (e.g. behavioural activation for depression; exposure therapy for phobias; contingency management for anorexia nervosa, substance use disorder)</td>
<td>Systematic Desensitization: mastering anxiety-provoking situations by approaching them gradually and in a relaxed state that limits anxiety Flooding: confronting feared stimulus for prolonged periods until it is no longer frightening Positive Reinforcement: strengthening behaviour and causing it to occur more frequently by rewarding it Negative Reinforcement: causing behaviour to occur more frequently by removing a noxious stimulus when desired behaviour occurs Extinction: causing a behaviour to diminish by not rewarding it Punishment (aversion therapy): causing a behaviour to diminish by applying a noxious stimulus</td>
<td>Individuals with motivation to change and specific symptoms that are amenable to change Global areas of dysfunction such as personality disorder are difficult to treat with behavioural therapy Usually short term (weeks-months)</td>
<td>12-20 wk</td>
</tr>
<tr>
<td>Cognitive Therapy</td>
<td>Depression, anxiety, panic disorder, personality disorders, and somatoform disorders</td>
<td>Moods/emotions are influenced by one’s thoughts and psychiatric disturbances are often caused by habitual errors in thinking With therapy, help patient make explicit their inaccurate automatic thoughts and correct assumptions with a more balanced perspective Uses thought records (often charts with column headings including “situation,” “feeling,” “thought,” “cognitive distortion”) to help monitor thoughts, the situations they occur in, and the feelings they might provoke due to their underlying cognitive errors</td>
<td>Motivated patients who will comply with homework, openness to changing core beliefs First course - usually 15 - 25 weeks Maintenance therapy can be carried out over years</td>
<td>First course - usually 15 - 25 weeks Maintenance therapy can be carried out over years</td>
</tr>
</tbody>
</table>
Table 14. Summary of Psychotherapeutic Modalities (continued)

<table>
<thead>
<tr>
<th>Type</th>
<th>Indications</th>
<th>Approach, Technique and Theory</th>
<th>Ideal Candidates</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Behavioural Therapy</td>
<td>Most mental health disorders including: mood, anxiety, OCD, personality, eating, substance use, psychotic disorders</td>
<td>Combines theory and method from Cognitive and Behavioural therapies to teach the patient to change connections between thinking patterns, habitual behaviours and mood/anxiety problems</td>
<td>Individuals with motivation to change and are able to participate in homework</td>
<td>Typically 6-18, 1hr sessions Maintenance sessions can be added over time</td>
</tr>
<tr>
<td>Dialectical Behavioural Therapy</td>
<td>Borderline Personality Disorder</td>
<td>Therapy that combines CBT techniques with Buddhist Zen mindfulness practices and dialectical philosophy Focusses on 4 types of skills: mindfulness, emotion regulation, interpersonal effectiveness, and distress tolerance Involves 4 components: individual therapy, group skills training, phone consultations, and a consultation team</td>
<td>Patients with severe problems of emotional dysregulation, impulsivity, and self-harm Patients with borderline personality disorder or borderline personality traits</td>
<td>Typically 1 yr</td>
</tr>
<tr>
<td>Motivational Interviewing</td>
<td>Substance use disorders Techniques can be applied to facilitate behavioural change in most psychological problems</td>
<td>Spirit of MI (CAPE): Compassion, Acceptance, Partnership,Evocation Principles of MI (RULE): Resist “righting reflex”, Understand client and their reasons for change, Listen, Empower by conveying hope and supporting autonomy Techniques of MI (DARS): Open-ended questions, Affirmations to validate client, Reflections (the skill of accurate empathy), Summaries to help client organize self</td>
<td>Patients with problematic substance use, maladaptive behaviour patterns (therapy disengagement, medication noncompliance, poor health habits)</td>
<td>Brief interventions (efficacy with as little as 15 min, single sessions), better result with more sessions, Addiction is a chronic condition, often need boosters over time</td>
</tr>
<tr>
<td>Motivational Enhancement Therapy (MET)</td>
<td></td>
<td></td>
<td></td>
<td>MET = 4 sessions</td>
</tr>
</tbody>
</table>

Other Therapies

- group psychotherapy
  - aims to promote self-understanding, acceptance, social skills
- family therapy
  - family system considered more influential than individual especially for children
  - focus on here and now, re-establishing parental authority, strengthening normal boundaries, and rearranging alliances
- narrative psychotherapy
  - an integrative approach that attempts to understand the patients experience as a whole
- hypnosis: mixed evidence for the treatment of pain, phobias, anxiety, and smoking cessation
  - mindfulness-based cognitive therapy (MBCT)/stress reduction (MBSR): derived from Buddhist meditative and philosophical practices; aims to help people attend to thoughts, behaviours and emotions non-judgmentally and in the moment using guided breathing exercises exercising evidence for adjustment disorder, MDD, anxiety, pain disorders, insomnia, substance relapse prevention

Pharmacotherapy

Antipsychotics

- “antipsychotics” and “neuroleptics” are terms used interchangeably
- overall mechanism of action: block, to varying degrees, dopamine activity in target brain pathways (see sidebar)
- indications: for calm, sleep, psychosis and mania reduction, mood stabilizing - used in schizophrenia and other psychotic disorders, mood disorders with or without psychosis, violent behaviour, autism, Tourette’s, somatoform disorders, dementia, OCD
- onset: immediate calming effect and decrease in agitation; thought disorder responds in 2-4 wk
- rational use
  - no reason to combine antipsychotics
  - choosing an antipsychotic
    - all antipsychotics are equally effective, except for clozapine (considered to be most effective in treatment-refractory psychoses)
    - atypical antipsychotics (SGA) are as effective as typical (first generation) antipsychotics but are thought to have better side effect profiles
    - choose a drug that the patient has responded to in the past or that was used successfully in a family member
- route: PO, short-acting or long-acting depot IM injections, sublingual
- if no response in 4-6 weeks, switch drugs; if response, titrate dose
- duration: minimum 6 mo, usually for life

Dopamine Pathways Affected by Antipsychotics

<table>
<thead>
<tr>
<th>Pathway</th>
<th>Effects</th>
<th>Associated Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mesolimbic</td>
<td>Emotion origination, reward</td>
<td>HIGH dopamine causes positive symptoms of schizophrenia (delusions, hallucinations)</td>
</tr>
<tr>
<td>Mesocortical</td>
<td>Cognition, executive function</td>
<td>LDV dopamine causes negative symptoms of schizophrenia</td>
</tr>
<tr>
<td>Nigrostriatal</td>
<td>Movement</td>
<td>LDV dopamine causes EPS</td>
</tr>
<tr>
<td>Tuberoinfundibular</td>
<td>Prolactin hormone release</td>
<td>LDV dopamine causes hyperprolactinemia</td>
</tr>
</tbody>
</table>
Long-Acting Preparations
- antipsychotics formulated in oil for IM injection (see Table 15)
- received on an outpatient basis
- indications: individuals with schizophrenia or other chronic psychosis who relapse because of non-adherence
- dosing: start at low dosages, then titrate every 2 to 4 wk to maximize safety and minimize side effects
- should be exposed to oral form prior to first injection
- side effects: risk of EPS, parkinsonism, increased risk of NMS

Canadian Guidelines for the Treatment of Acute Psychosis in the Emergency Setting
- haloperidol 5 mg IM (or loxapine 25 mg) ± lorazepam 2 mg IM
- olanzapine 2.5-10 mg (PO, IM, quick dissolve)
- risperidone 2 mg (M-tab, liquid)

Table 15. Common Antipsychotic Agents

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Starting Dose</th>
<th>Maintenance</th>
<th>Maximum</th>
<th>Relative Potency (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Typicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol (Haldol(^{\text{a}}))</td>
<td>2.5 mg IM q4-8h 0.5-5 mg PO b/tid 0.2 mg/kg/d PO</td>
<td>Based on clinical effect</td>
<td>20 mg/d PO</td>
<td>2</td>
</tr>
<tr>
<td>Fluphenazine enanthate (Moditen(^{\text{a}}), Modenate(^{\text{a}}) for IM formulation)</td>
<td>2.5-10 mg/d PO 1.5 mg PO qhs 25 mg IM/SC q1-3wk</td>
<td>20 mg/d PO</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol HCl (Clopixol(^{\text{a}}))</td>
<td>20-30 mg/d PO 20-40 mg/d PO</td>
<td>100 mg/d PO</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol acetate (Acuphase(^{\text{a}}))</td>
<td>50-150 mg IM q48-72h</td>
<td>400 mg IM (q2wk)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zuclopenthixol decanoate (Cloxpitol Depot(^{\text{a}}))</td>
<td>100 mg IM q1-4wk 150-300 mg IM q2wk</td>
<td>600 mg IM/wk</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine (Trilafon(^{\text{a}}))</td>
<td>8-16 mg PO b/tid 4-8 mg PO t/qid</td>
<td>64 mg/d PO</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Loxapine HCl (Loxitane(^{\text{a}}))</td>
<td>10 mg PO tid 12.5-50 mg IM q4-6h</td>
<td>250 mg/d PO</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine (Largactil(^{\text{a}}))</td>
<td>10-25 mg PO b/t/qid 400 mg/d PO</td>
<td>1000 mg/d PO</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td><strong>Atypicals</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone (Risperdal(^{\text{a}}), Risperdal Consta(^{\text{a}}) for IM long acting preparation, Risperdal(^{\text{a}}) M-Tab for melting form – placed on tongue)</td>
<td>1-2 mg OD/bid 4-8 mg/d PO 25 mg IM q2wk</td>
<td>8 mg/d PO</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Paliperidone (Invega(^{\text{a}}))</td>
<td>3 mg/d PO 3-12 mg/d PO</td>
<td>12 mg/d PO</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Olanzapine (Zyprexa(^{\text{a}}), Zyprexa Zydis(^{\text{a}}) for melting form – placed on tongue, Zyprexa Intramuscular(^{\text{a}}))</td>
<td>5 mg/d PO 10-20 mg/d PO 30 mg/d PO</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asenapine (Saphris(^{\text{a}}))</td>
<td>5 mg SL bid 5-10 mg SL bid</td>
<td>10 mg bid</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Ziprasidone (Zeldox(^{\text{a}}))</td>
<td>20 mg bid PO 40-80 mg bid PO</td>
<td>160 mg/d PO</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole (Abilify(^{\text{a}}))</td>
<td>10-15 mg/d PO 10-15 mg/d PO</td>
<td>30 mg/d PO</td>
<td>7.5</td>
<td></td>
</tr>
<tr>
<td>Quetiapine (Seroquel(^{\text{a}}), Seroquel XR(^{\text{a}}) for extended release(^{\text{a}}))</td>
<td>25 mg PO bid 400-800 mg/d PO</td>
<td>800 mg/d PO</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Clozapine (Clozaril(^{\text{a}}))</td>
<td>25 mg PO bid 300-600 mg/d PO</td>
<td>600 mg/d PO</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Typical (First Generation) vs. Atypical (Second Generation) Antipsychotics

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Typical</th>
<th>Atypical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Block postsynaptic dopamine receptors (D2)</td>
<td>Block postsynaptic dopamine receptors (D2)</td>
<td></td>
</tr>
<tr>
<td>Block serotonin receptors (5-HT2) on presynaptic dopaminergic terminals, triggering dopamine release, and reversing dopamine blockade in some pathways</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pros
- Inexpensive
- Plenty of injectable forms available
- Fewer EPS
- Low risk of tardive syndromes
- Mood stabilizing effects

Cons
- More EPS
- Tardive syndromes in long-term use
- Not mood stabilizing
- Expensive
- Few injectable forms available
- Metabolic side effects (weight gain, hyperglycemia, lipid abnormalities, metabolic syndrome)
- Extravagant (or new onset) of obsessive behaviour

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

*NEJM* 2005;353:1209-23

**Study:** Randomized, double-blind, active-control trial with median follow-up of 6 mo.

**Patients:** 1,432 patients with a diagnosis of schizophrenia (as per DSM-IV criteria) and able to take antipsychotic medications (as determined by study doctors). Mean age 41, 74% male, 26% female.

**Intervention:** 1-4 capsules daily of olanzapine (20.1 mg), quetiapine (45.3 mg), risperidone (3.9 mg), perphenazine (20.8 mg), or ziprasidone (11.2 mg), with dosage at the discretion of the study doctor. Mean modal doses in parentheses.

**Main Outcome:** Discontinuation of treatment for any cause.

**Results:** Olanzapine group had statistically significant lower rate of discontinuation for any cause (44%) from all others (quetiapine – 82%, risperidone – 74%, perphenazine – 75%, ziprasidone – 79%). There were no significant differences in time until discontinuation due to intolerable side effects; however, olanzapine was associated with a significantly higher rate of metabolic side effects.
### Table 16. Commonly Used Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone (Risperdal&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Lower incidence of EPS than typical antipsychotics at lower doses (&lt;8 mg)</td>
<td>SE: insomnia, agitation, EPS, H/A, anxiety, prolactin, postural hypotension, constipation, dizziness, weight gain</td>
<td>Quick dissolve (IM-formulations available)</td>
</tr>
<tr>
<td>Olanzapine (Zyprexa&lt;sup&gt;®&lt;/sup&gt;, Zydis&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Better overall efficacy compared to haloperidol</td>
<td>SE: mild sedation, insomnia, dizziness, minimal anticholinergic, early AST and ALT elevation, restlessness, high risk of metabolic effects (weight gain, DM, hyperlipidemia)</td>
<td>Quick dissolve formulation (Zydis&lt;sup&gt;®&lt;/sup&gt;) used commonly in ER setting for better compliance IM form available</td>
</tr>
<tr>
<td>Quetiapine (Seroquel&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Associated with less weight gain compared to clozapine and olanzapine</td>
<td>SE: H/A, sedation, dizziness, constipation</td>
<td>Weekly blood counts for at least 1 mo, then q2wk</td>
</tr>
<tr>
<td>Clozapine (Clozaril®)</td>
<td>Most effective for treatment-resistant schizophrenia</td>
<td>Most sedating of first line atypicals</td>
<td>Do not use with drugs which may cause bone marrow suppression due to risk of agranulocytosis</td>
</tr>
<tr>
<td>Aripiprazole (Abilify&lt;sup&gt;®&lt;/sup&gt;)</td>
<td>Less weight gain and risk of metabolic syndrome compared to olanzapine and a lower incidence of EPS compared to haloperidol</td>
<td>SE: H/A, agitation, anxiety, insomnia, weight gain, decreased serum prolactin levels</td>
<td>Weekly blood counts for at least 1 mo, then q2wk</td>
</tr>
</tbody>
</table>

### Table 17. Side Effects of Antipsychotics

<table>
<thead>
<tr>
<th>System</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic</td>
<td>Dry mouth, urinary retention, constipation, blurred vision, toxic-confusional states</td>
</tr>
<tr>
<td>α-adrenergic Blockade</td>
<td>Orthostatic hypotension, impotence, failure to ejaculate</td>
</tr>
<tr>
<td>Dopaminergic Blockade</td>
<td>Extrapyramidal syndromes, galactorrhea, amenorrhea, impotence, weight gain</td>
</tr>
<tr>
<td>Anti-histamine</td>
<td>Sedation</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Agranulocytosis (clozapine)</td>
</tr>
<tr>
<td>Hypersensitivity Reactions</td>
<td>Liver dysfunction, blood dyscrasias, skin rashes, neuroleptic malignant syndrome, altered temperature regulation (hypothyroidism or hyperthermia)</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Metabolic syndrome</td>
</tr>
</tbody>
</table>

#### Neuroleptic Malignant Syndrome

- **psychiatric emergency**
  - due to massive dopamine blockade; increased incidence with high potency and depot neuroleptics
- **risk factors**
  - medication factors: sudden increase in dosage, starting a new drug
  - patient factors: medical illness, dehydration, exhaustion, poor nutrition, external heat load, male, young adults
- **clinical presentation**
  - mental status changes (usually occur first), fever, autonomic reactivity, rigidity
  - develops over 24-72 h
  - labs: increased creatine phosphokinase, leukocytosis, myoglobinuria
- **treatment**: supportive - discontinue drug, hydration, cooling blankets, dantrolene (hydrantoin derivative, used as a muscle relaxant), bromocriptine (DA agonist)
- **mortality**: 5%

#### Extrapyramidal Symptoms

- incidence related to increased dose and potency
- acute (early-onset; reversible) vs. tardive (late-onset; often irreversible)
Table 18. Extrapyramidal Symptoms

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Presentation</th>
<th>Onset</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute: Young Asian and Black males</td>
<td>Sustained abnormal posture; torsions, twisting, contraction of muscle groups; muscle spasms (e.g. oculogyric crisis, laryngospasm, torticollis)</td>
<td>Acute: within 5 d</td>
<td>Acute: benzotropine or diphenhydramine</td>
</tr>
<tr>
<td>Elderly females</td>
<td>Motor restlessness; crawling sensation in legs relieved by walking; very distressing, increased risk of suicide and poor adherence</td>
<td>Acute: within 10 d</td>
<td>Acute: bromazepam, propranolol, or diphenhydramine; reduce or change neuroleptic to lower potency</td>
</tr>
<tr>
<td>Elderly females</td>
<td>Tremor, rigidity (cogwheeling); akinesia; postural instability (increased/absent arm-swing, stooped posture, shuffling gait, difficulty pivoting)</td>
<td>Acute: &gt;90 d</td>
<td>Acute: benzotropine (or benzodiazepine if side effects); reduce or change neuroleptic to lower potency</td>
</tr>
<tr>
<td>If third episode, elderly, psychotic features, refractory depression, &gt;2 episodes in 5 yr</td>
<td>Purposeless, constant movements, involving facial and mouth musculature, or less commonly – the limbs</td>
<td>Tardive: &gt;90 d</td>
<td>Tardive: no good treatment; may try clozapine; discontinue drug or reduce dose</td>
</tr>
</tbody>
</table>

Antiparkinsonian Agents (Anticholinergic Agents)

- **types**
  - benztropine (Cogentin®) 2 mg PO, IM or IV OD (~1-6 mg)
  - amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)
  - diphenhydramine (Benadryl®) 25-50 mg PO/IM qid
  - amantadine (Symmetrel®) 100 mg PO bid (100-400 mg)

- do not always prescribe with neuroleptics
- give antiparkinsonian agents only if at high risk for acute EPS or if acute EPS develops
- do not give these for tardive syndromes because they worsen the condition

Antidepressants

- **onset of effect**
  - relief of neurovegetative (physical) symptoms: 1-3 wk
  - relief of emotional/cognitive symptoms: 2-6 wk

- taper TCAs slowly (over weeks-months) because they can cause withdrawal reactions
- tapering of any kind of antidepressant is usually required and based on the half-life of the medication and the patient's individual sensitivity (e.g. fluoxetine does not require a slow taper due to long half life)

- it is important to be particularly vigilant over the first 2 wk of therapy as neurovegetative symptoms may start to resolve while emotional and cognitive symptoms may not (patients may be particularly at risk for suicidal behaviour during this time; in children/adolescents, paroxetine and venlafaxine not prescribed for this reason, as increases restlessness and suicidal ideation)

- treatment of bipolar depression
  - monotherapy with antidepressants is not advisable as a switch from depression to mania can occur
  - patients with bipolar disorder should only be treated with an antidepressant if it is combined with a mood stabilizer or antipsychotic

Table 19. Common Antidepressants

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Daily Starting Dose (mg)</th>
<th>Therapeutic Dose (mg)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>SSRI</td>
<td>fluoxetine (Prozac®)</td>
<td>20</td>
<td>20-80</td>
<td>Useful for anxiety states, OCD, eating disorders, seasonal depression, typical and atypical depression</td>
</tr>
<tr>
<td></td>
<td>fluvoxamine (Luvox®)</td>
<td>50-100</td>
<td>150-300</td>
<td>All SSRIs have similar effectiveness but consider side effect profiles and half-lives</td>
</tr>
<tr>
<td></td>
<td>paroxetine (Paxil®)</td>
<td>10</td>
<td>20-60</td>
<td>Sertraline, citalopram, and escitalopram have the least drug-interactions and are sleep-wake neutral</td>
</tr>
<tr>
<td></td>
<td>sertraline (Zolof®)</td>
<td>50</td>
<td>50-200</td>
<td>Fluoxetine and paroxetine are the most activating drugs (recommend taking in the AM)</td>
</tr>
<tr>
<td></td>
<td>citalopram (Celexa®)</td>
<td>20</td>
<td>20-40</td>
<td>Fluoxetine does not require a taper due to long half-life and is the most used in children as it has most evidence</td>
</tr>
<tr>
<td></td>
<td>escitalopram (Cipralex®)</td>
<td>10</td>
<td>10-20</td>
<td>Fluvoxamine is sedating (should be taken with PM)</td>
</tr>
<tr>
<td>SNRI</td>
<td>venlafaxine (Effexor®)</td>
<td>37.5-75</td>
<td>75-225</td>
<td>Useful for depression, anxiety disorders</td>
</tr>
<tr>
<td></td>
<td>duloxetine (Cymbalta®)</td>
<td>40</td>
<td>40-60</td>
<td>No significant difference when choosing.</td>
</tr>
<tr>
<td>NDRI</td>
<td>bupropion (Wellbutrin®)</td>
<td>100</td>
<td>300-450</td>
<td>Useful for depression, seasonal depression</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Causes less sexual dysfunction (may reverse effects of SSRIs/SNRIs), weight gain, and sedation</td>
</tr>
<tr>
<td>TCA (3rd Amines)</td>
<td>amitriptyline (Elavil®)</td>
<td>75-100</td>
<td>150-300</td>
<td>Use for OCD (clomipramine), melancholic depression</td>
</tr>
<tr>
<td></td>
<td>imipramine (Tofran®)</td>
<td>75-100</td>
<td>150-300</td>
<td>Contraindicated with history of seizure, stroke brain tumour, brain injury, closed head injury</td>
</tr>
<tr>
<td>TCA (2nd Amines)</td>
<td>nortriptyline (Aventyl®)</td>
<td>75-100</td>
<td>75-150</td>
<td>Not recommended for anxiety disorder treatment because of stimulating effects</td>
</tr>
<tr>
<td></td>
<td>desipramine (Norpramin®)</td>
<td>100-200</td>
<td>150-300</td>
<td>Important to specify formulation, as available in IR, SR, XL (longest)</td>
</tr>
<tr>
<td>MAOI</td>
<td>phenelzine (Nardil®)</td>
<td>45</td>
<td>60-90</td>
<td>Useful for moderate/severe depression that does not respond to SSRI, atypical depression</td>
</tr>
<tr>
<td></td>
<td>tranylcypromine (Parnate®)</td>
<td>30</td>
<td>10-60</td>
<td>No significant difference when choosing.</td>
</tr>
<tr>
<td>RIMA</td>
<td>moclobemide (Manerix®)</td>
<td>300</td>
<td>300-600</td>
<td>Useful for depression unresponsive to other therapies</td>
</tr>
<tr>
<td>NASSA</td>
<td>mirtazapine (Remeron®)</td>
<td>15</td>
<td>15-45</td>
<td>Useful in depression with prominent features of insomnia, agitation, or cachexia</td>
</tr>
</tbody>
</table>

**Notes**: MAOI = monoamine oxidase inhibitors; NASSA = noradrenergic and specific serotonergic antagonists; NDRI = norepinephrine and dopamine reuptake inhibitors; RIMA = reversible inhibition of MAO-A; SNRI = serotonin and norepinephrine reuptake inhibitors; SSR = selective serotonin reuptake inhibitors; TCA = tricyclic antidepressants
Treatment Approach for Depression

- **optimization**: ensuring adequate drug doses for the individual
- **augmentation**: the addition of a medication that is not considered an antidepressant to an antidepressant regimen (e.g. thyroid hormone, lithium, atypical antipsychotics [specifically: olanzapine, risperidone, aripiprazole])
- **combination**: the addition of another antidepressant to an existing treatment regimen (e.g. the addition of bupropion to an SSRI or SNRI)
- **substitute**: change in the primary antidepressant (within or outside a class)
- **note**: it is important to fully treat the symptoms of depression in order to decrease rates and severity of relapses

### Table 20. Features of Commonly Used Antidepressant Classes

<table>
<thead>
<tr>
<th></th>
<th>SSRI</th>
<th>SNRI</th>
<th>TCA</th>
<th>MAOI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Examples</strong></td>
<td>Fluoxetine, Sertraline, Citalopram</td>
<td>Venlafaxine, Duloxetine</td>
<td>Amitriptyline, Clomipramine</td>
<td>Phenelzine</td>
</tr>
<tr>
<td><strong>Mode of Action</strong></td>
<td>Block serotonin reuptake only</td>
<td>Block norepinephrine and serotonin reuptake</td>
<td>Block norepinephrine and serotonin reuptake</td>
<td>Irreversible inhibition of monoamine oxidase A and B</td>
</tr>
<tr>
<td><strong>Side Effects</strong></td>
<td>Fewer than TCA, therefore increased compliance&lt;br&gt;CNS: restlessness, tremor, insomnia, headache, drowsiness&lt;br&gt;GI: N/V, diarrhea, abdominal cramps, weight loss&lt;br&gt;Sexual dysfunction: impotence, anorgasmia&lt;br&gt;CVS: increased HR, conduction delay, serotonin syndrome, EPS, SIADH</td>
<td>Low dose side effects include insomnia (serotonergic)&lt;br&gt;Higher dose side effects include: tremors, tachycardia, sweating, insomnia, dose-dependent increase in diastolic BP (noradrenergic)&lt;br&gt;Anticholinergic effects: (see Table 17)&lt;br&gt;Noradrenergic effects: tremors, tachycardia, sweating, insomnia, erectile and ejaculation problems α-1 adrenergic effects: orthostatic hypotension&lt;br&gt;Antihistamine effects: sedation, weight gain&lt;br&gt;CNS: sedation, stimulation, ↓ seizure threshold&lt;br&gt;CVS: ↑ HR, conduction delay</td>
<td>Anticholinergic effects:&lt;br&gt;(see Table 17)&lt;br&gt;Noradrenergic effects: tremors, tachycardia, sweating, insomnia, erectile and ejaculation problems&lt;br&gt;α-1 adrenergic effects: orthostatic hypotension&lt;br&gt;Antihistamine effects: sedation, weight gain&lt;br&gt;CNS: sedation, stimulation, ↓ seizure threshold</td>
<td>Hypertensive crises with tyramine rich foods (e.g. wine, cheese), headache, flushes, palpitations, N/V, photophobia&lt;br&gt;Dizziness, reflex tachycardia, postural hypotension, sedation, insomnia&lt;br&gt;Weight gain&lt;br&gt;Social dysfunction&lt;br&gt;Energizing&lt;br&gt;Minimal anticholinergic and antihistamine effects</td>
</tr>
<tr>
<td><strong>Risk in Overdose</strong></td>
<td>Relatively safe in OD</td>
<td>Tachycardia and N/V seen in acute overdose</td>
<td>3 times therapeutic dose is lethal&lt;br&gt;Presentation: anticholinergic effects, CNS stimulation, then depression and seizures&lt;br&gt;ECG: prolonged QT (duration reflects severity)&lt;br&gt;Treatment: activated charcoal, cathartics, supportive treatment, IV diazepam for seizure, physostigmine salicylate for coma&lt;br&gt;Do not give ipecac, as can cause rapid neurologic deterioration and seizures</td>
<td>Toxic in OD, but wider margin of safety than TCA</td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>SSRIs inhibit P450 enzymes, therefore will affect levels of drugs metabolized by P450 system</td>
<td>Does not seem to inhibit P450 system</td>
<td>MAOI, SSRI</td>
<td>EtOH</td>
</tr>
<tr>
<td></td>
<td>MAOI, SSRI</td>
<td>EtOH</td>
<td>Hypertensive crises with noradrenergic medications (e.g. TCA, decongestants, amphetamines)&lt;br&gt;Serotonin syndrome with serotonic drugs (e.g. SSRI, tryptophan, dextromethorphan)</td>
<td></td>
</tr>
</tbody>
</table>
Table 20. Features of Commonly Used Antidepressant Classes (continued)

<table>
<thead>
<tr>
<th>Examples</th>
<th>NDRI</th>
<th>RIMA</th>
<th>NASSA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buproprion</td>
<td>Block norepinephrine and dopamine</td>
<td>Reversible inhibitor of monoamine oxidase A</td>
<td>Enhance central noradrenergic and serotonergic activity by inhibiting pre-synaptic α-2 adrenergic receptors</td>
</tr>
<tr>
<td>Moclobemide</td>
<td>Leads to ↑ norepinephrine and serotonin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td>Risk of fatal overdose when combined with citalopram or clomipramine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Serotonin Syndrome
- thought to be due to over-stimulation of the serotonergic system
- can result from medication combinations such as SSRI+MAOI, SSRI+tryptophan, MAOI+meperidine, MAOI+tryptophan
- rare but potentially life-threatening adverse reaction to SSRIs, especially when switching from an SSRI to an MAOI
- symptoms include nausea, diarrhea, palpitations, chills, restlessness, confusion, and lethargy but can progress to myoclonus, hyperthermia, rigor and hypertonicity
- treatment: discontinue medication and administer emergency medical care as needed
- important to distinguish from NMS

Discontinuation Syndrome
- caused by the abrupt cessation of an antidepressant
- observed most frequently with paroxetine, fluvoxamine, and venlafaxine (drugs with shortest half-lives)
- symptoms usually begin within 1-3 d and include: anxiety, insomnia, irritability, mood lability, N/V, dizziness, headache, dystonia, tremor, chills, fatigue, lethargy, and myalgia
- treatment: symptoms may last between 1-3 wk, but can be relieved within 24 h by restarting antidepressant therapy at the same dose the patient was taking and initiating a slow taper over several weeks
- consider using a drug with a longer half-life such as fluoxetine

Mood Stabilizers

General Prescribing Information
- examples: lithium, lamotrigine, divalproex, carbamazepine
- used in conjunction with atypical antipsychotics for managing episodes of bipolar disorder - depression, mania, stabilization
- vary in their ability to "treat" (reduce symptoms acutely) or "stabilize" (prevent relapse and recurrence) manic and depressive symptoms; multi-agent therapy is common
- before initiating, get baseline: CBC, ECG (if patient >45 yr old or cardiovascular risk), urinalysis, BUN, Cr, electrolytes, TSH
- before initiating lithium: screen for pregnancy, thyroid disease, seizure disorder, neurological, renal, cardiovascular diseases
- full effects not for 2-4 wks, thus may need acute coverage with benzodiazepines or antipsychotics

Specific Prescribing Information
- detailed pharmacological guidelines available online from the Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD)
- for clinical information for treating bipolar disorder (see Mood Disorders, PS9)
## Table 21. Commonly Used Mood Stabilizers

<table>
<thead>
<tr>
<th>Indications</th>
<th>Lithium</th>
<th>Lamotrigine (Lamictal®)</th>
<th>Divalproex (Epival®)</th>
<th>Carbamazepine (Tegretol®)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st line:</td>
<td>Acute mania (monotherapy or with adjunct SGA)</td>
<td>Bipolar I depression (monotherapy)</td>
<td>Acute mania (monotherapy or with adjunct SGA)</td>
<td>Acute mania (monotherapy)</td>
</tr>
<tr>
<td>Other uses:</td>
<td>Bipolar II depression</td>
<td>Augmentation of antidepressants in MDE and OCD</td>
<td>Bipolar disorder maintenance (monotherapy or with adjunct SGA)</td>
<td>Bipolar disorder maintenance (monotherapy or in combination with lithium)</td>
</tr>
<tr>
<td>Mode of Action</td>
<td>Unknown</td>
<td>May inhibit 5-HT3 receptors</td>
<td>Depresses synaptic transmission</td>
<td>Depresses synaptic transmission</td>
</tr>
<tr>
<td>Dosage</td>
<td>Adult: 600-1500 mg/d</td>
<td>Starting: 12.5-15 mg/d</td>
<td>750-2500 mg/d</td>
<td>400-1600 mg/d</td>
</tr>
<tr>
<td>Therapeutic Level</td>
<td>Adult: 0.8-1.0 mmol/L (1.0-1.25 mmol/L for acute mania)</td>
<td>Therapeutic plasma level not established</td>
<td>17-50 mmol/L</td>
<td>350-700 µmol/L</td>
</tr>
<tr>
<td>Side Effects</td>
<td>GI: N/V, diarrhea, stomach pain</td>
<td>GI: N/V, diarrhea</td>
<td>GI: liver dysfunction, N/V, diarreha</td>
<td>GI: N/V, diarrhea, hepatic toxicity</td>
</tr>
<tr>
<td>Lithium Toxicity</td>
<td>• clinical diagnosis as toxicity can occur at therapeutic levels</td>
<td>• general causes</td>
<td>• CNS: ataxia, dizziness, deliria, headache, somnolence</td>
<td>• CNS: ataxia, dizziness, slurred speech, drowsiness, confusion, vertigo, diplopia</td>
</tr>
<tr>
<td>• common causes: overdose, sodium/fluid loss, concurrent medical illness</td>
<td>• clinical presentation</td>
<td>• Other: hair loss, weight gain, transient thrombocytopenia, neural tube defects when used in pregnancy</td>
<td>• Hematologic: transient leukopenia (10%), agranulocytosis, aplastic anemia</td>
<td></td>
</tr>
<tr>
<td>• management</td>
<td>• discontinue lithium for several doses and begin again at a lower dose when lithium level has fallen to a non-toxic range</td>
<td>• Other: anxiety</td>
<td>• Skin: rash (5% risk; should discontinue drug because of risk of Stevens-Johnson syndrome)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• serum lithium levels, BUN, electrolytes</td>
<td>• Other: liver loss, weight gain, transient thrombocytopenia, neural tube defects when used in pregnancy</td>
<td>• Other: neural tube defects when used in pregnancy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• saline infusion</td>
<td>• Other: liver loss, weight gain</td>
<td>• Hematologic: transient leukopenia (10%), agranulocytosis, aplastic anemia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• hemodialysis if lithium &gt;2 mmol/L, coma, shock, severe dehydration, failure to respond to treatment after 24 h, or deterioration</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Anxiolytics

- anxiolytics mask or alleviate symptoms; they do not cure them
- **indications**
  - short-term treatment of transient forms of anxiety disorders, insomnia, alcohol withdrawal (especially delirium tremens), barbiturate withdrawal, organic brain syndrome (acute agitation in delirium), EPS and akathisia due to antipsychotics, seizure disorders, musculoskeletal disorders
- **relative contraindications**
  - major depression (except as an adjunct to other treatment), history of drug/alcohol abuse, caution in pregnancy/breastfeeding
- **mechanism of action**
  - benzodiazepines: potentiate binding of GABA to its receptors; results in decreased neuronal activity
  - buspirone: partial agonist of 5-HT1A receptors

Benzodiazepines

- should be used for limited periods (weeks-months) to avoid dependence
- all benzodiazepines are sedating; be wary with use in the elderly
- have similar efficacy, so choice depends on half-life, metabolites and route of administration, OD or bid
- taper slowly over weeks-months because they can cause withdrawal reactions
  - low dose withdrawal: tachycardia, HTN, panic, insomnia, anxiety, impaired memory and concentration, perceptual disturbances
  - high dose withdrawal: hyperpyrexia, seizures, psychosis, death
- avoid alcohol because of potentiation of CNS depression; caution with drinking and driving/machinery use
- **side effects**
  - CNS: drowsiness, cognitive impairment, reduced motor coordination, memory impairment
  - physical dependence, tolerance
- **withdrawal**
  - symptoms: anxiety, insomnia, autonomic hyperactivity (less common)
  - onset: 1-2 d (short-acting), 2-4 d (long-acting)
  - duration: weeks-months
  - complications with above 50 mg diazepam/day: seizures, delirium, arrhythmias, psychosis
  - management: taper with long-acting benzodiazepine
  - similar to but less severe than alcohol withdrawal; can be fatal
- **overdose**
  - commonly used drug in overdose
  - overdose is rarely fatal
  - benzodiazepines are more dangerous and may cause death when combined with alcohol, other CNS depressants or TCAs

Benzodiazepine Antagonist – Flumazenil (Anexate®)

- use for suspected benzodiazepine overdose
- specific antagonist at the benzodiazepine receptor site

Buspirone (Buspar®)

- **primary use**: GAD
- may be preferred over benzodiazepines because are non-sedating, no interaction with alcohol, does not alter seizure threshold, not prone to abuse
- **onset of action**: 2 wk
- **side effects**: dizziness, drowsiness, nausea, headache, nervousness, EPS
### Table 22. Common Anxiolytics

<table>
<thead>
<tr>
<th>Class</th>
<th>Drug</th>
<th>Dose Range (mg/d)</th>
<th>t1/2 (h)</th>
<th>Appropriate Use</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-acting</td>
<td>clonazepam (Rivotril®)</td>
<td>0.25-4</td>
<td>18-50</td>
<td>Akathisia, generalized anxiety, seizure prevention, panic disorder</td>
</tr>
<tr>
<td></td>
<td>diazepam (Valium®)</td>
<td>2-40</td>
<td>30-100</td>
<td>Generalized anxiety, seizure prevention, muscle relaxant, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>chlordiazepoxide (Librium®)</td>
<td>5-300</td>
<td>30-100</td>
<td>Sleep, anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>flurazepam (Dalmane®)</td>
<td>15-30</td>
<td>50-160</td>
<td>Sleep</td>
</tr>
<tr>
<td>Short-acting</td>
<td>alprazolam (Xanax®)</td>
<td>0.25-4.0</td>
<td>6-20</td>
<td>Panic disorder, high dependency rate</td>
</tr>
<tr>
<td></td>
<td>lorazepam (Ativan®)</td>
<td>0.5-6.0</td>
<td>10-20</td>
<td>Sleep, generalized anxiety, akathisia, alcohol withdrawal, sublingual available for very rapid action</td>
</tr>
<tr>
<td></td>
<td>oxazepam (Serax®)</td>
<td>10-120</td>
<td>8-12</td>
<td>Sleep, generalized anxiety, alcohol withdrawal</td>
</tr>
<tr>
<td></td>
<td>temazepam (Restoril®)</td>
<td>7.5-30</td>
<td>8-20</td>
<td>Sleep</td>
</tr>
<tr>
<td></td>
<td>triazolam (Halcion®)</td>
<td>0.125-0.5</td>
<td>1.5-5</td>
<td>Shortest t1/2, rapid sleep, but rebound insomnia</td>
</tr>
<tr>
<td><strong>Azapirones</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>buspirone (Buspar®)</td>
<td>20-60</td>
<td>2-11</td>
<td>Generalized anxiety</td>
</tr>
<tr>
<td></td>
<td>zopiclone (Imovane®)</td>
<td>5-7.5</td>
<td>3.8-6.5</td>
<td>Sleep</td>
</tr>
</tbody>
</table>

### Somatic Therapies

#### Electroconvulsive Therapy

- Various methodological improvements have been made since the first treatment in 1938 to reduce adverse effects
- Modern ECT: induction of a generalized seizure using an electrical pulse through scalp electrodes while the patient is under general anesthesia with a muscle relaxant
- Considerations: unilateral vs. bilateral electrode placement, pulse rate, dose, number and spacing of treatments
- Usual course is 6-12 treatments, 2-3 treatments per wk
- Indications:
  - Depression refractory to adequate pharmacological trial (MDD or Bipolar I depression)
  - High suicide risk
  - Medical risk in addition to depression (dehydration, electrolytes, pregnancy)
  - Previous good response to ECT
  - Familial response to ECT
  - Elderly
  - Psychotic depression
  - Catatonic features
  - Marked vegetative features
  - Acute schizophrenia unresponsive to medication
  - Mania unresponsive to medications
  - OCD refractory to conventional treatment
- Side effects: risk of anesthesia, memory loss (may be retrograde and/or anterograde, tends to resolve by 6-9 mo, permanent impairment controversial), headaches, myalgias
- Unilateral ECT causes less memory loss than bilateral but may not be as effective
- Contraindications: increased intracranial pressure, recent (< 2 wk) MI (not absolute but requires special monitoring)

#### Magnetic Seizure Therapy (MST)

- Early studies demonstrate efficacy for depression as well as anxiety, reduced memory side effects vs. ECT

### ECT in Society

Prior to the 1940's, ECT was performed without the use of muscle relaxants, resulting in seizures with full-scale convulsions and rare but serious complications such as vertebral and long-bone fractures. This practice may have led to negative societal perceptions of ECT, further perpetuated by barbaric depictions in popular culture. Despite ongoing stigmatization, ECT as it is practiced today is an effective and safe option for patients struggling with mental illness.

### Efficacy of ECT in Depression: A Meta-Analytic Review

*J of ECT* 2004; 20:13-20

**Study**: Meta-analysis of randomized and non-randomized control trials.

**Patients**: Individuals with unipolar and bipolar depression.

**Methods**: MEDLINE search for relevant papers from 1966-2003.

**Main Outcomes**: The Hamilton Depression Rating scale was used to determine response to treatment.

**Results**: ECT was found to be superior to simulated ECT, placebo, TCA's, MAOIs, and anti-depressants in general.

**Summary**: ECT is an efficacious treatment modality, particularly in severe and treatment-resistant depression.
Repetitive Transcranial Magnetic Stimulation (rTMS)

- noninvasive production of focal electrical currents in select brain areas using magnetic induction
- **indications**: strong evidence for treatment-resistant depression, pain disorders; possibly efficacious for anxiety disorders, eating disorders, substance use disorders
- **adverse effects**: common - transient local discomfort, hearing issues, cognitive changes; rare - seizure, syncope, mania induction

Neurosurgical Treatments

Ablative/Lesion Procedures

- used for intractable MDD or OCD, efficacy ranges from 25-75% depending on procedure
- **adverse effects**: related to lesion location and size, high risk of suicide in those who are not helped by surgery

Deep Brain Stimulation

- placement of small electrode leads in specific brain areas to alter neuronal signaling, usually for intractable MDD
- response rates (>50% symptom reduction) of 40-70%, adverse effects related to surgical risks and poor treatment response

Vagus Nerve Stimulation

- direct, intermittent electrical stimulation of left cervical vagus nerve via implanted pulse generator
- used for chronic, recurrent MDD that has failed previous therapy and ECT; slow onset, approximately 30% response rate at 1 yr

Other Therapy Modalities

Phototherapy (Light Box Therapy)

- bright light source exposure, best in morning, for 30-60 minutes (usually 10,000 lux)
- proposed mechanisms: reverses pathological alterations in circadian rhythm through action on suprachiasmatic nucleus
- **indications**: SAD, non-seasonal depression (as augmentation), sleep disorders
- **adverse effects**: mania induction, reaction with photosensitizing drug or photosensitive eye or skin conditions

Aerobic Exercise

- moderate-intense aerobic exercise is associated with acute increased secretion of serotonin, phenethylamine, BDNF, endogenous opioids and cannabinoids (likely this combination is what contributes to the “runner’s high”)
- long term increases gray matter in multiple areas, as well as improvements in cognition, memory and stress tolerance
- **indications**: ongoing research suggests efficacy as adjunctive treatment for MDD; may be helpful in PTSD, schizophrenia
## Canadian Legal Issues

### Common Forms

**Table 23. Common Forms Under the Mental Health Act (in Ontario)**

<table>
<thead>
<tr>
<th>Form</th>
<th>Who Signs</th>
<th>When</th>
<th>Expiration Date</th>
<th>Right of Patient to Review Board Hearing</th>
<th>Options Before Form Expires</th>
</tr>
</thead>
<tbody>
<tr>
<td>Form 1: Application by physician to hospitalize a patient for psychiatric assessment against his/her will to a schedule 1 facility (Form 42 given to patient)</td>
<td>Any MD</td>
<td>Within 7 d after examination of the patient</td>
<td>72 h after hospitalization Void if not implemented within 7 d</td>
<td>No</td>
<td>Form 3 + 30 or voluntary admission or Send home ± follow-up</td>
</tr>
<tr>
<td>Form 2: Order for a psychiatric assessment against his/her will which is ordered by Justice of the Peace</td>
<td>Justice of the Peace</td>
<td>No statutory time restriction</td>
<td>7 d from when completed Purpose of form is complete once patient brought to hospital</td>
<td>No</td>
<td>Form 1 + 42 or Send home ± follow-up</td>
</tr>
<tr>
<td>Form 3: Certificate of involuntary admission to a schedule 1 facility (Form 30 given to patient, notice to rights advisor)</td>
<td>Attending MD (different than MD who completed Form 1)</td>
<td>Before expiration of Form 1</td>
<td>14 d</td>
<td>Yes</td>
<td>Form 4 + 30 or Voluntary admission (Form 5)</td>
</tr>
<tr>
<td>Form 4: Certificate of renewal of involuntary admission to a schedule 1 facility (original Form 30 given to patient, notice to rights advisor)</td>
<td>Attending MD following patient on Form 3</td>
<td>Prior to expiration of Form 3</td>
<td>First: 1 mo Second: 2 mo Third: 3 mo (max)</td>
<td>Yes</td>
<td>Form 4 + 30 or Voluntary admission (Form 5)</td>
</tr>
<tr>
<td>Form 5: Change to informal/voluntary status</td>
<td>Attending MD following patient on Form 3/4</td>
<td>Whenever deemed appropriate</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Form 30: Notice to patient that they are now under involuntary admission on either Form 3 or 4. Original to the patient, copy to chart</td>
<td>Attending MD</td>
<td>Whenever Form 3 or Form 4 filled</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
<tr>
<td>Form 33: Notice to patient that patient is incapable of consenting to treatment of mental disorder, and/or management of property and/or disclosure of health information (original copy to patient)</td>
<td>Attending MD</td>
<td>Whenever deemed appropriate</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
</tr>
</tbody>
</table>

* Schedule 1 Facilities: Able to provide intensive inpatient and outpatient care

---

### Consent

- see *Ethical, Legal, and Organizational Medicine, ELOAM7*
Community Treatment Order (CTO)

- purpose: a CTO orders a person suffering from a serious mental disorder to receive treatment and supervision in the community. Based on a comprehensive plan outlining medications, appointments, and other care believed necessary to allow the person to live in the community (vs. in a psychiatric facility, where things are more restrictive)
- intended for those who
  - due to their serious mental disorder, experience a pattern of admission to a psychiatric facility where condition is usually stabilized
  - after being released, these patients often lack supervision and stop treatment, leading to destabilization
  - due to the destabilization of their condition, these patients usually require re-admission to hospital
  - if CTO violated (e.g. treatment not taken), patient brought in by police to hospital for treatment as per CTO
- criteria for a physician to issue a CTO
  - patient with a prior history of hospitalization
  - a community treatment plan for the person has been made
  - examination by a physician within the previous 72 h before entering into the CTO plan
  - ability of the person subject to the CTO to comply with it
  - consultation with a rights advisor and consent of the person or the person’s substitute decision maker
- CTOs are valid for 6 mo unless they are renewed or terminated at an earlier date such as:
  - where the person fails to comply with the CTO
  - when the person or his/her substitute decision-maker withdraws consent to the community treatment plan
- CTO process is consent-based and all statutory protections governing informed consent apply
- the rights of a person subject to a CTO include
  - the right to a review by the Consent and Capacity Board with appeal to the courts each time a CTO is issued or renewed
  - a mandatory review by the Consent and Capacity Board every second time a CTO is renewed
  - the right to request a re-examination by the issuing physician to determine if the CTO is still necessary for the person to live in the community
  - the right to review findings of incapacity to consent to treatment
  - provisions for rights advice

Duty to Inform/Warn

- see Ethical, Legal, and Organizational Medicine, ELOAM6
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**Acronyms**

- A-a: alveolar-arterial
- A-D0: alveolar-arterial oxygen diffusion gradient
- ABG: arterial blood gas
- ACEI: angiotensin converting enzyme inhibitor
- ACV: assist-control ventilation
- AESOPD: acute exacerbation of COPD
- AF: acid-fast bacillus
- AFT: alpha-fibrinogen
- ALS: amyotrophic lateral sclerosis
- ANA: antinuclear antibody
- ANCA: anti-neutrophil cytoplasmic antibody
- APPT: activated partial thromboplastin time
- ARDS: acute respiratory distress syndrome
- ASA: acetylsalicylic acid (Aspirin®)
- ARDs: acute respiratory distress syndrome
- ATS: acetylsalicylic acid (Aspirin®)
- AV: arteriovenous
- AVM: arteriovenous malformation
- COP: cryptogenic organizing pneumonia
- CO: cardiac output
- CI: cardiac index
- CF: cystic fibrosis
- CD: Crohn’s disease
- CA: cancer
- CCS: calcium channel blocker
- CF: cystic fibrosis
- CG block: circumflex block
- CHF: congestive heart failure
- CI: cardiac index
- CD: chronic obstructive pulmonary disease
- COP: chronic obstructive pulmonary disease
- COPD: chronic obstructive pulmonary disease
- CPAP: continuous positive airway pressure
- CSA: central sleep apnea
- CVD: cardiovascular disease
- CVP: central venous pressure
- CVP: coal worker’s pneumoconiosis
- DC: disseminated intravascular coagulation
- DLCO: carbon monoxide diffusing capacity of lung
- EBUS: endobronchial ultrasound
- ECMO: extracorporeal membrane oxygenation
- ERV: expiratory reserve volume
- ETT: endotracheal tube
- FEV1: forced expiratory volume in 1 second
- FEF: forced expiratory flow rate
- FiO2: fraction of oxygen in inspired air
- FRC: functional residual capacity
- FO2: fraction of oxygen in inspired air
- FIO2: fraction of inspired oxygen
- GLM: glomerular basement membrane
- H/A: headache
- H: hypothyroidism
- HLA: hypothyroidism
- HRT: hormone replacement therapy
- IBD: inflammatory bowel disease
- IC: insulin-dependent diabetes mellitus
- IC: insulin-dependent diabetes mellitus
- ICS: inhaled corticosteroid
- ICP: intracranial pressure
- IC: inspiratory capacity
- IPF: idiopathic pulmonary fibrosis
- IPP: idiopathic pulmonary fibrosis
- IC: inspiratory capacity
- LVEDD: left ventricular end diastolic diameter
- LVEDP: left ventricular end diastolic pressure
- LV: left ventricle
- LV: left ventricular failure
- MAC: Mycobacterium avium complex
- MDR: metronidazole
- MEP: maximum expiratory pressure
- MIP: minimum inspiratory pressure
- NSAID: nonsteroidal anti-inflammatory drug
- NSC: normal saline
- NPPV: non-invasive positive pressure ventilation
- PA: pulmonary arterial pressure
- Pao2: arterial partial pressure of oxygen
- PaCO2: arterial partial pressure of carbon dioxide
- PaCO2: arterial partial pressure of carbon dioxide
- Pao2: arterial partial pressure of oxygen
- PCWP: pulmonary capillary wedge pressure
- PE: pulmonary embolism
- PEEP: positive end expiratory pressure
- PET: pulmonary embolism
- PFT: pulmonary function tests
- PMNs: polymorphonuclear cells
- PP: pulse pressure
- PSV: positive pressure ventilation
- PTH: parathyroid hormone
- PTT: partial thromboplastin time
- PV: pulmonary venous pressure
- RAV: right atrial volume
- RAP: right atrial pressure
- RBBB: right bundle branch block
- RF: rheumatoid factor
- RV: residual volume
- RVEDV: right ventricular end diastolic volume
- RVSP: right ventricular systolic pressure
- RVH: right ventricular hypertension
- SC: squamous cell carcinoma
- SCL: small cell lung cancer
- SV: stroke volume
- SVC: superior vena cava
- SVR: systemic vascular resistance
- TCA: tricyclic antidepressant
- TLF: total lung capacity
- TAC: total arterial compliance
- TC: total parenteral nutrition
- UC: ulcerative colitis
- UN: upper urinary tract infection
- VD: ventilation-perfusion
- VATS: video-assisted thoracoscopic surgery
- VCP: ventilatory capacity
- VCSS: ventilatory capacity
- VTE: venous thromboembolism
- V wave: venous return
- V1: tidal volume

**Basic Anatomy Review**

Figure 1. Lung lobes and bronchi

Figure 2. Respiration patterns in normal and disease states
## Differential Diagnoses of Common Presentations

### Table 1. Differential Diagnosis of Dyspnea

**Acute Dyspnea (minutes-hours)**
- **Cardiac causes**
  - Ischemic heart disease
  - CHF exacerbation
  - Cardiac tamponade
- **Pulmonary causes**
  - Upper airway obstruction (anaphylaxis, foreign body)
  - Airway disease (asthma, COPD exacerbation, bronchitis)
  - Parenchymal lung disease (ARDS, pneumonia)
  - Pulmonary vascular disease (PE, vasculitis)
  - Pleural disease (pneumothorax, tension pneumothorax)
  - Respiratory control (metabolic acidosis, ASA toxicity)

**Psychiatric causes**
- Anxiety/psychosomatic

### Table 2. Differential Diagnosis of Chest Pain

**Nonpleuritic**
- **Pulmonary**
  - Pneumonia
  - PE
  - Neoplasm
- **Cardiac**
  - MI
  - Myocarditis/pericarditis
- **Esophageal**
  - GERD
  - Spasm
  - Esophagitis
  - Ulceration
  - Achalasia
  - Neoplasm
  - Esophageal rupture

**Mediastinal**
- Lymphoma
- Thymoma

**Subdiaphragmatic**
- PUD
- Gastritis
- Biliary colic
- Pancreatitis

**Vascular**
- Dissecting aortic aneurysm

**MSK**
- Costochondritis
- Skin
- Breast
- Ribs

**Pleuritic**
- **Pulmonary**
  - Pneumonia
  - PE
  - Neoplasm
- **Cardiac**
  - Heart failure
  - Mitral valve disease
  - Pneumothorax
  - Empyema
- **GI**
  - Subphrenic abscess
  - Pancreatitis

### Table 3. Differential Diagnosis of Hemoptysis

- **Airway Disease**
  - Acute or chronic bronchitis
  - Bronchiectasis
  - Bronchogenic CA
  - Bronchial carcinoid tumour

- **Parenchymal Disease**
  - Pneumonia
  - TB
  - Lung abscess

- **Vascular Disease**
  - PE
  - Elevated pulmonary venous pressure:
  - LVF
  - Mitral stenosis
  - Vascular malformation
  - Vasculitis
  - Goodpasture’s syndrome
  - Idiopathic pulmonary hemosiderosis

- **Miscellaneous**
  - Impaired coagulation
  - Pulmonary endometriosis

### Table 4. Differential Diagnosis of Cough

- **Airway Irritants**
  - Inhaled smoke, dusts, fumes
  - Postnasal drip (upper airway cough syndrome)
  - Aspiration
  - Gastric contents (GERD)
  - Oral secretions
  - Foreign body

- **Airway Disease**
  - URTI including postnasal drip and sinusitis
  - Acute or chronic bronchitis
  - Bronchiectasis
  - Neoplasm
  - External compression by node or mass lesion
  - Asthma
  - COPD

- **Parenchymal Disease**
  - Pneumonia
  - Lung abscess
  - Interstitial lung disease
  - CHF
  - Drug-induced (e.g., ACEI)

---

Adapted from: Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008. With permission from Elsevier
Pulmonary Function Tests

• useful in differentiating the pattern of lung disease (obstructive vs. restrictive)
• assess lung volumes, flow rates, and diffusion capacity (Figures 5A and 5B)
• note: normal values for FEV$_1$ are approximately ±20% of the predicted values (for age, sex, and height); ethnicity may affect predicted values

| Table 5. Comparison of Lung Flow and Volume Parameters in Obstructive vs. Restrictive Lung Disease |
|-----------------------------------|-----------------------------------|
| **Obstructive**                   | **Restrictive**                   |
| Decreased flow rates (most marked during expiration) | Decreased lung compliance |
| Air trapping (increased RV/TLC)   | Decreased lung volumes           |
| Hyperinflation (increased FRC, TLC) |                                |

<table>
<thead>
<tr>
<th>DDx</th>
<th>ILD, pleural disease, neuromuscular disease, chest wall disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$/FVC</td>
<td>↓ or N</td>
</tr>
<tr>
<td>TLC</td>
<td>↓ or N</td>
</tr>
<tr>
<td>RV</td>
<td>↓ or N</td>
</tr>
<tr>
<td>RV/TLC</td>
<td>N</td>
</tr>
<tr>
<td>DLCO</td>
<td>↓ or N</td>
</tr>
</tbody>
</table>

*Bronchiectasis can be obstructive or mixed

<table>
<thead>
<tr>
<th>Table 6. Common Respirology Procedures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Technique</td>
</tr>
<tr>
<td>Plethysmography (<em>body box</em>)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>He dilution</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Bronchoscopy</td>
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<tr>
<td></td>
</tr>
</tbody>
</table>

Figure 4. Signs of respiratory distress

In addition to the above:
• Abdominal Breathing
• Increased RR
• Central/peripheral cyanosis
• Inability to speak

Figure 5A. Subcompartments of lung volumes

Figure 5B. Expiratory flow volume curves

Adapted with permission from Elsevier. Weinberger SE. Principles of pulmonary medicine, 5th ed. 2008

Lung Volumes
ERV  –  Expiratory Reserve Volume
FEF  –  Forced Expiratory Flow Rate
FEV$_1$  –  Forced Expiratory Volume (in one second)
FRC  –  Functional Residual Capacity
IC  –  Inspiratory Capacity
RV  –  Residual Volume
TLC  –  Total Lung Capacity
VC  –  Vital Capacity
V$_T$  –  Tidal Volume
Figure 6. Interpreting PFTs

Chest X-Rays
- see Medical Imaging, MI4

Table 7. CXR Patterns and Differential Diagnosis

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Signs</th>
<th>Common DDx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consolidation</td>
<td>Air bronchogram</td>
<td>Acute: water (pulmonary edema), pus (pneumonia), blood (hemorrhage)</td>
</tr>
<tr>
<td>(&quot;Airspace disease&quot;)</td>
<td>Silhouette sign</td>
<td>Chronic: neoplasm (lymphoma), inflammatory (eosinophilic pneumonia), infection (TB, fungal)</td>
</tr>
<tr>
<td></td>
<td>Less visible blood vessels</td>
<td></td>
</tr>
<tr>
<td>Reticular</td>
<td>Increased pulmonary markings</td>
<td>ILD (IPF, collagen vascular disease, asbestos, drugs)</td>
</tr>
<tr>
<td>(&quot;Interstitial disease&quot;)</td>
<td>Honeycombing (IPF)</td>
<td></td>
</tr>
<tr>
<td>Nodular</td>
<td>Cavitary vs. non-cavitary</td>
<td>Cavitary: neoplasm (primary vs. metastatic lung cancer), infectious (anaerobic or Gram negative, TB, fungal), inflammatory (RA, Granulomatosis with Polyangitis [GPA]) Non-cavitary: above + sarcoïd, Kaposi’s sarcoma (in HIV), silicosis and other pneumoconioses</td>
</tr>
</tbody>
</table>

Arterial Blood Gases
- provides information on acid-base and oxygenation status
- see Nephrology, NP14

Approach to Acid-Base Status
1. Is the pH acidemic (pH <7.35), alkalemic (pH >7.45), or normal (pH 7.35-7.45)?
2. What is the primary disturbance?
   - metabolic: change in HCO₃⁻ and pH in same direction
   - respiratory: change in HCO₃⁻ and pH in opposite directions
3. Is there appropriate compensation? (see Table 8)
   - metabolic compensation occurs over 2-3 d reflecting altered renal HCO₃⁻ production and excretion
   - respiratory compensation through ventilatory control of P₇,CO₂ occurs immediately
   - inadequate compensation may indicate a second acid-base disorder

Figure 7. Oxygen-Hb dissociation curve

Factors that Shift the Oxygen-Hb Dissociation Curve to the Right
"CADET, face right!"
CO₂
Acid
2,3-DPG
Exercise
Temperature (increased)
### Table 8. Expected Compensation for Specific Acid-Base Disorders

<table>
<thead>
<tr>
<th>Disturbance</th>
<th>PaCO₂ (mmHg) (normal ~40)</th>
<th>HCO₃⁻ (mmHg) (normal ~24)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Acidosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↑ 10</td>
<td>↑ 1</td>
</tr>
<tr>
<td>Chronic</td>
<td>↑ 10</td>
<td>↑ 3</td>
</tr>
<tr>
<td><strong>Respiratory Alkalosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↓ 10</td>
<td>↓ 2</td>
</tr>
<tr>
<td>Chronic</td>
<td>↓ 10</td>
<td>↓ 5</td>
</tr>
<tr>
<td><strong>Metabolic Acidosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↓ 1</td>
<td>↓ 1</td>
</tr>
<tr>
<td><strong>Metabolic Alkalosis</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute</td>
<td>↑ 5-7</td>
<td>↑ 10</td>
</tr>
</tbody>
</table>

4. If there is metabolic acidosis, what is the anion gap and osmolar gap?
   - anion gap = |Na⁺| – (|Cl⁻| + |HCO₃⁻|); normal ≤ 10-15 mmol/L
   - osmolar gap = measured osmolarity – calculated osmolarity = measured – (2|Na⁺| + glucose + urea); normal ≤ 10 mmol/L

5. If anion gap is increased, is the change in bicarbonate the same as the change in anion gap?
   - if not, consider a mixed metabolic picture

### Table 9. Differential Diagnosis of Respiratory Acidosis

<table>
<thead>
<tr>
<th>Increased PaCO₂ secondary to hypoventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiratory Centre Depression (Decreased RR)</strong></td>
</tr>
<tr>
<td>Drugs (anesthesia, sedatives, narcotics)</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Increased ICP</td>
</tr>
<tr>
<td>Encephalitis</td>
</tr>
<tr>
<td>Stroke</td>
</tr>
<tr>
<td>Central apnea</td>
</tr>
<tr>
<td>Supplemental O₂ in chronic CO₂ retainers (e.g. COPD)</td>
</tr>
<tr>
<td><strong>Neuromuscular Disorders (Decreased Vital Capacity)</strong></td>
</tr>
<tr>
<td>Myasthenia gravis</td>
</tr>
<tr>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Poliomyelitis</td>
</tr>
<tr>
<td>Muscular dystrophies</td>
</tr>
<tr>
<td>ALS</td>
</tr>
<tr>
<td>Myopathies</td>
</tr>
<tr>
<td>Chest wall disease (obesity, kyphoscoliosis)</td>
</tr>
<tr>
<td><strong>Airway Obstruction (Asthma, COPD)</strong></td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Pulmonary edema</td>
</tr>
<tr>
<td>Pneumothorax</td>
</tr>
<tr>
<td>Pneumonia</td>
</tr>
<tr>
<td>ILD (late stage)</td>
</tr>
<tr>
<td>ARDS</td>
</tr>
</tbody>
</table>

### Table 10. Differential Diagnosis of Respiratory Alkalosis

<table>
<thead>
<tr>
<th>Decreased PaCO₂ secondary to hyperventilation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypoxemia</strong></td>
</tr>
<tr>
<td>Pulmonary disease (pneumonia, edema, PE, interstitial fibrosis)</td>
</tr>
<tr>
<td>Severe anemia</td>
</tr>
<tr>
<td>Heart failure</td>
</tr>
<tr>
<td>High altitude</td>
</tr>
<tr>
<td><strong>Respiratory Centre Stimulation</strong></td>
</tr>
<tr>
<td>CNS disorders</td>
</tr>
<tr>
<td>Gram-negative sepsis</td>
</tr>
<tr>
<td>Drugs (ASA, progesterone, theophylline, catecholamines, psychotropics)</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
<tr>
<td>Anxiety</td>
</tr>
<tr>
<td>Pain</td>
</tr>
</tbody>
</table>

| **Mechanical Hyperventilation (Excessive Mechanical Ventilation)** |

- see Nephrology: NP15 for differential diagnosis of metabolic acidosis and alkalosis

---

**ABG Normal Values**
- pH 7.35-7.45
- HCO₃⁻ 22-26 mEq/L
- PaCO₂ 35-45 mm Hg
- PaO₂ 80-100 mm Hg

Acidosis ↔ Hyperkalemia
Alkalosis ↔ Hypokalemia

Note: Mixed acid-base disturbances can still have a "normal" pH

Osmolar Gap = measured osmolarity – calculated osmolarity; for calculated osmolarity think "2 salts and a sticky BUN" (2Na + glucose + urea)

**Anion Gap Metabolic Acidosis**
- MUDPILES CAT
  - Methanol
  - Uremia
  - Diabetic ketoacidosis/starvation
  - Ketaacidosis
  - Phenformin/Paraldehyde
  - Isoniazid, Iron, Ibuprofen
  - Lactate
  - Ethylene glycol
  - Salicylates
  - Cyanide, Carbon dioxide
  - Alcoholic ketoacidosis
  - Toluene, Theophylline
**Diseases of Airway Obstruction**

### Pneumonia
- see [Infectious Diseases], ID7

### Asthma
- see [Family Medicine], FM16 and [Pediatrics], P89

**Definition**
- chronic inflammatory disorder of the airways resulting in episodes of reversible bronchospasm causing airflow obstruction
- associated with reversible airflow limitation and airway hyper-responsiveness to endogenous or exogenous stimuli

**Epidemiology**
- common, 7-10% of adults, 10-15% of children
- most children with asthma significantly improve in adolescence
- often family history of atopy (asthma, allergic rhinitis, eczema)
- occupational asthma (organic allergies, isocyanates, animals, etc.)
Pathophysiology
- airway obstruction \( \rightarrow \) V/Q mismatch \( \rightarrow \) hypoxemia \( \rightarrow \) ↑ ventilation \( \rightarrow \) ↓ \( P_{CO2} \) \( \rightarrow \) ↑ pH and muscle fatigue \( \rightarrow \) ↓ ventilation, ↑ \( P_{CO2} \)/↓ pH

Signs and Symptoms
- dyspnea, wheezing, chest tightness, cough (especially nocturnal), sputum
- symptoms can be paroxysmal or persistent
- signs of respiratory distress (see Figure 4)
- pulsus paradoxus

Table 11. Criteria for Determining if Asthma is Well Controlled

| Criteria                                                                 | Well Controlled
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Daytime symptoms &lt;4 d/wk</td>
<td>No asthma-related absence from work/school</td>
</tr>
<tr>
<td>Night-time symptoms &lt;1 night/wk</td>
<td>( \beta_2 )-agonist use &lt;4 times/wk</td>
</tr>
<tr>
<td>Physical activity normal</td>
<td>FEV1 or PEF &gt;90% of best</td>
</tr>
<tr>
<td>Exacerbations mild, infrequent</td>
<td>PEF diurnal variation &lt;10-15%</td>
</tr>
</tbody>
</table>

Adapted from: Can Respir J 2012; 19:127-184

Investigations
- \( O_2 \) saturation
- ABCs (consist in acute exacerbation, along with peak flows, in Emergency Department)
  - decreased \( P_{O2} \) during attack (V/Q mismatch)
  - decreased \( P_{CO2} \) in mild asthma (hyperventilation)
  - normal or increased \( P_{CO2} \) is an ominous sign: patient is no longer able to hyperventilate (worsened airway obstruction or respiratory muscle fatigue)
- PFTs (do when stable)

Table 12. Pulmonary Function Criteria for Diagnosis of Asthma

<table>
<thead>
<tr>
<th>Preferred Measurement</th>
<th>Alternative Measurements</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spirometry Showing Reversible Airway Obstruction</td>
<td>Peak Expiratory Flow Variability</td>
</tr>
<tr>
<td>(1) ( \Delta ) FEV1/FVC below lower limit of normal (&lt;0.75 to 0.8 ) in adults, (&lt;0.9 ) in children age 6+</td>
<td>(1) ( \uparrow ) in PEF after a bronchodilator or course of controller therapy</td>
</tr>
<tr>
<td>AND</td>
<td>Adults: PEF ( \uparrow ) 60 L/min (min. 20% OR Diurnal variation &gt;8% for twice daily readings (20% for multiple daily readings)</td>
</tr>
<tr>
<td>(2) ( \uparrow ) FEV1 ( \geq )12% (min. 200 mL in adults) after bronchodilator or controller therapy</td>
<td>Children age 6+: PEF ( \uparrow ) 20%</td>
</tr>
</tbody>
</table>

Positive Challenge Test
(1) Methacholine challenge: PC20 \( <4 \) mg/mL \( (4-16 \) mg/mL is borderline; \( >16 \) mg/mL is negative) OR
(2) Post-exercise: \( \downarrow \) FEV1 \( \geq \)10-15%

Adapted from: Can Respir J 2012; 19:127-184

Treatment
- environment: avoid triggers
- patient education: features of the disease, goals of treatment, self-monitoring
- pharmacological
  - symptomatic relief in acute episodes: short-acting \( \beta_2 \)-agonist, anticholinergic bronchodilators, oral steroids, addition of a long acting \( \beta_2 \)-agonist
  - long-term prevention: inhaled/oral corticosteroids, anti-allergic agents, long-acting \( \beta_2 \)-agonists, methylxanthine, LTRA, anti-IgE antibodies (e.g. Xolair®)

Emergency Management of Asthma (see Emergency Medicine, ER29)
1. inhaled \( \beta_2 \)-agonist first line (MDI route and spacer device recommended)
2. systemic steroids (PO or IV if severe)
3. if severe add anticholinergic therapy ± magnesium sulphate
4. rapid sequence intubation in life-threatening cases (plus 100% \( O_2 \) monitors, IV access)
5. SC/IV adrenaline if caused by anaphylaxis, IV salbutamol if unresponsive
6. corticosteroid therapy at discharge

Asthma Triggers
- URTIs
- Allergens (pet dander, house dust, molds, cockroach)
- Irritants (cigarette smoke, air pollution)
- Drugs (NSAIDs, \( \beta \)-blockers)
- Preservatives (sulphites, MSG)
- Other (emotion/anxiety, cold air, exercise, GERD)

Signs of Poor Asthma Control
DANGERS
Daytime Sx >4 times/wk
Activities reduced
Nighttime Sx >1 time/wk
GP visits
ER visits
Rescue puffer (SABA) use >4 times/wk
School and work absences

Consider LABA for night-time symptoms

LTRA in Addition to Usual Care for Acute Asthma in Adults and Children
Cochrane DB Syst Rev 2012;CD006100
Purpose: To determine if the addition of LTRA is beneficial to patients with acute asthma receiving inhaled bronchodilators and systemic corticosteroids.
Methods: RCTs in Cochrane Airways Group’s Specialised Register of trials that compared LTRA and standard vs. placebo and standard in people with acute asthma of any age.
Results: 8 trials, 1,470 adults and 470 children. For oral treatment, no significant difference between LTRAs and control in hospital admission (RR 0.86; 95% CI 0.75-0.98) or requirement for additional care (RR 0.87; 95% CI 0.61-1.26). LTRAs improved FEV1 in adults (mean difference 0.08, 95% CI 0.01-0.14) but not in children. No significant difference in adverse events between LTRAs and control (RR 0.81; 95% CI 0.23-2.90). Similar results were found for intravenous treatment.
Conclusions: Currently, there is no evidence to support routine use of LTRAs in acute asthma.

Natural Progression of COPD
40s
- Chronic productive cough, wheezing occasionally
50s
- 1st acute chest illness
60s
- Dyspnea on exertion, increasing sputum, more frequent exacerbations

Late
- Hypoxemia with cyanosis,
- Stage polythemia, hypercapnia (morning headache), cor pulmonale, weight loss

GOLD Classification of the Severity of COPD
GOLD 1 Mild FEV1 >80% of predicted
GOLD 2 Moderate 50% ≤ FEV1 <80% of predicted
GOLD 3 Severe 30% ≤ FEV1 <50% of predicted
GOLD 4 Very Severe FEV1 <30% of predicted
Guidelines for Asthma Management

Figure 10. Guidelines for asthma management

- Regularly Reassess
  - Control
  - Spirometry or PEF
  - Inhaler technique
  - Adherence
  - Triggers
  - Comorbidities
  - Sputum eosinophils

- Adjust Therapy to Achieve and Maintain Control
  - Prednisone
  - Inhaled Corticosteroid (ICS)

- SABA on Demand
- SABA or ICS/LABA* on Demand

Environmental Control, Education, and Written Action Plan

Confirm Diagnosis

Chronic Obstructive Pulmonary Disease

- Definition
  - Progressive and irreversible condition of the lung characterized by chronic obstruction to airflow with many patients having periodic exacerbations, gas trapping, lung hyperinflation, and weight loss
  - 2 subtypes: chronic bronchitis and emphysema (usually coexist to variable degrees)
  - Gradual decrease in FEV1 over time with episodes of acute exacerbations

Table 13. Clinical and Pathologic Features of COPD*

<table>
<thead>
<tr>
<th>Chronic Bronchitis</th>
<th>Emphysema</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Defined Clinically</strong></td>
<td></td>
</tr>
<tr>
<td>Productive cough on most days for at least 3 consecutive months in 2 successive years</td>
<td></td>
</tr>
<tr>
<td>Obstruction is due to narrowing of the airway lumen by mucosal thickening and excess mucus</td>
<td></td>
</tr>
<tr>
<td><strong>Defined Pathologically</strong></td>
<td></td>
</tr>
<tr>
<td>Dilution and destruction of air spaces distal to the terminal bronchiole without obvious fibrosis</td>
<td></td>
</tr>
<tr>
<td>Decreased elastic recoil of lung parenchyma causes decreased expiratory driving pressure, airway collapse, and air trapping</td>
<td></td>
</tr>
<tr>
<td><strong>2 Types</strong></td>
<td></td>
</tr>
<tr>
<td>1) Centriacinar (respiratory bronchioles predominantly affected)</td>
<td></td>
</tr>
<tr>
<td>Typical form seen in smokers, primarily affects upper lung zones</td>
<td></td>
</tr>
<tr>
<td>2) Panacinar (respiratory bronchioles, alveolar ducts, and alveolar saccs affected)</td>
<td></td>
</tr>
<tr>
<td>Accounts for about 1% of emphysema cases</td>
<td></td>
</tr>
<tr>
<td>α1-antitrypsin deficiency, primarily affects lower lobes</td>
<td></td>
</tr>
</tbody>
</table>

Note: Table 13 includes Clinical and Pathologic Features of COPD.*

Risk Factors

- Smoking is #1 risk factor

- Others
  - Environmental: air pollution, occupational exposure, exposure to wood smoke or other biomass fuel for cooking
  - Treatable factors: α1-antitrypsin deficiency, bronchial hyperactivity
  - Demographic factors: age, family history, male sex, history of childhood respiratory infections, low socioeconomic status

Pulmonary Embolism in Patients with Unexplained Exacerbation of COPD: Prevalence and Risk Factors

- Study: Prospective cohort study of 211 patients with COPD (all current and former smokers) admitted to hospital for severe COPD exacerbation of unknown origin
- Measurements: All patients received spiral CT angiogram (CTA) and various compression ultrasonography of both legs
- Results: 25% of patients met diagnostic criteria for PE (± CTA or ± US)
- Conclusions: Prevalence of PE in patients hospitalized for COPD exacerbation of unknown origin is 25%. Therefore, all patients presenting to hospital with COPD exacerbation without obvious cause require PE workup (leg dopplers or CTA – decision of which to use depends on pre-test probability of the patient)

Non-Invasive Positive Pressure Ventilation for Treatment of Respiratory Failure due to Exacerbations of COPD

- Study: Cochrane Systematic Review, 14 RCTs
- Population: 758 adult patients with COPD and acute respiratory failure due to COPD exacerbation
- Intervention: Usual medical care (UMC) and Non-invasive positive ventilation (NPPV) vs. UMC alone
- Primary Outcome: Treatment failure, mortality, and tracheal intubation
- Results: The risks for all primary outcomes were reduced with NPPV use: treatment failure (RR 0.49); mortality (RR 0.52); and intubation use (RR 0.81). Length of hospital stay was a significant mean 3.4 days shorter, but no difference between ICU length of stay. There is a small and significant improvement in pH (weight mean difference (WMD)=0.04), PCO2 (WMD=-0.40 mm Hg), and respiratory rate (WMD=-3.08 bpm) within 1 h post-treatment with NPPV. Complications associated with treatment were reduced in the NPPV treatment arm (RR 0.30)
- Conclusion: For patients in respiratory failure due to a COPD exacerbation, NPPV is effective in reducing treatment failure, mortality, and need for intubation when used as a first line treatment adjunct to UMC.
Signs and Symptoms

Table 14. Clinical Presentation and Investigations for Chronic Bronchitis and Emphysema

<table>
<thead>
<tr>
<th>Signs</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyanosis (2° to hypoxemia and hypercapnia)</td>
<td>PFT: ↓ FEV1, ↓ FEV1/FVC, ↓ N TLC, ↓ or N DLCO</td>
</tr>
<tr>
<td>Peripheral edema from RVF (cor pulmonale)</td>
<td>CXR: AP diameter normal</td>
</tr>
<tr>
<td>Crackles, wheezes</td>
<td>↑ bronchovascular markings</td>
</tr>
<tr>
<td>Prolonged expiration if obstructive</td>
<td>Enlarged heart with cor pulmonale</td>
</tr>
<tr>
<td>Frequently obese</td>
<td></td>
</tr>
</tbody>
</table>

**Table 15. Treatment of Stable COPD**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking cessation</td>
<td>Nicotine replacement, bupropion, varenicline</td>
</tr>
<tr>
<td>Vaccination</td>
<td>Influenza, pneumococcal vaccine</td>
</tr>
<tr>
<td>Home oxygen</td>
<td>Prevents cor pulmonale and decreases mortality if used &gt;15h/d; indicated if (1) P O2 &lt; 55 mmHg or (2) ≤ 60 mmHg with cor pulmonale or polycythemia</td>
</tr>
</tbody>
</table>

**SYMPTOMATIC RELIEF (no mortality benefit)**

**Bronchodilators (mainstay of current drug therapy, used in combination)**

- Short-acting anticholinergics (e.g. ipratropium bromide) and short-acting β2-agonists (e.g. salbutamol, terbutaline)
  - LABAs (e.g. salmeterol, formoterol, indacaterol) and long-acting anticholinergics (e.g. tiotropium bromide, glycopyrronium bromide)
  - More sustained effects for moderate to severe COPD

**Inhaled corticosteroid (ICS) + LABA combination (e.g. Advair®: fluticasone + salmeterol, Symbicort®: budesonide + formoterol)**

| Theophylline: weak bronchodilator; limited evidence to suggest combination with bronchodilator |
| Side effects: nervous tremor, nausea/vomiting/diarrhea, tachycardia, arrhythmias, sleep changes |
| PDE4 inhibitor: roflumilast (Daxxas®) anti-inflammatory medication useful in COPD with chronic bronchitis, severe airflow obstruction, frequent exacerbations |

**Corticosteroids**

ICS therapy is contraindicated and ICS should only be used with a LABA in combination in patients with a history of exacerbations

COPD airways are usually inflamed but often not responsive to steroids, therefore avoid chronic systemic glucocorticoids (although oral steroids are very important when treating exacerbations)

**Surgical**

Lung volume reduction surgery (resection of emphysematous parts of lung, associated with higher mortality if FEV1 < 20%, lung transplant

**Other**

Patient education, eliminate respiratory irritants/allergens (occupational/environmental), exercise rehabilitation to improve physical endurance

*Note that the distinction between “blue bloaters” and “pink puffers” is more of historical than practical interest as most COPD patients have elements of both.

Table 15. Treatment of Stable COPD

**PROLONG SURVIVAL**

**Outcome:** Exacerbation rates, hospitalizations, mortality, lung function and adverse effects.

**Results:** In patients with COPD, inactive vaccine correlated with fewer exacerbations per vaccinated subject than placebo (weighted mean difference (WMD) -0.37, 95% CI -0.64 to -0.11). Inactivated vaccine resulted in fewer influenza-related infections than placebo (WMD 0.19, 95% CI 0.07-0.46). There was also an increased risk of local mild, transient adverse reactions with the vaccine.

**Conclusion:** There appears to be a reduction in influenza-related infections, as well as exacerbations in patients with COPD receiving the vaccine.

---

Remember to step down therapy to lowest doses which control symptoms/signs of bronchoconstriction

**Influenza Vaccine for Patients with Chronic Obstructive Pulmonary Disease**

**Study:** Cochrane Systematic Review, 11 RCTs included, 6 specifically in COPD patients.

**Population:** Six of the studies were done on COPD patients in particular, while the others were on elderly and high-risk individuals. Asthma patients were excluded.

**Intervention:** Live or inactivated virus vaccines vs. placebo.

**Outcome:** Exacerbation rates, hospitalizations, mortality, lung function and adverse effects.

**Results:** In patients with COPD, inactive vaccine correlated with fewer exacerbations per vaccinated subject than placebo (weighted mean difference (WMD) -0.37, 95% CI -0.64 to -0.11). Inactivated vaccine resulted in fewer influenza-related infections than placebo (WMD 0.19, 95% CI 0.07-0.46). There was also an increased risk of local mild, transient adverse reactions with the vaccine.

**Conclusion:** There appears to be a reduction in influenza-related infections, as well as exacerbations in patients with COPD receiving the vaccine.

**Different Durations of Corticosteroid Therapy for Exacerbations of Chronic Obstructive Pulmonary Disease**

**Study:** Cochrane systematic review, 8 studies, 326 patients, with severe or very severe COPD.

**Population:** 65% of included studies were in COPD patients.

**Intervention:** Long-term systemic corticosteroid treatment (n = 657; odds ratio (OR) 0.72, 95% confidence interval (CI) 0.46 to 1.14), which was equivalent to 22 fewer per 1000 for short-duration treatment (95% CI 19 fewer to 34 more). No difference in risk of relapse (a new event) was observed between short-duration and longer-duration systemic corticosteroid treatment (n = 493; OR 1.04, 95% CI 0.70 to 1.59), which was equivalent to nine fewer per 1000 for short-duration treatment (95% CI 68 fewer to 100 more). Time to the next COPD exacerbation did not differ in one large study that was powered to detect non-inferiority and compared five days versus 14 of systemic corticosteroid treatment (n = 311; hazard ratio 0.98, 95% CI 0.86 to 1.12). In five studies no difference in the likelihood of an adverse event was found between short-duration and longer-duration systemic corticosteroid treatment (n = 502; OR 0.89, 95% CI 0.46 to 1.79, or nine fewer per 1000 [95% CI 44 fewer to 51 more]). Length of hospital stay (n = 421; mean difference (MD) -0.61 days, 95% CI -1.51 to 0.28) and lung function at the end of treatment (n = 185; MD FEV1 -0.04 L; 95% CI -0.19 to 0.01) did not differ between short-duration and longer-duration treatment.

**Conclusion:** 5 d of oral corticosteroids is likely to be sufficient for treatment of adults with acute exacerbations of COPD, and this review suggests that the likelihood is low that shorter courses of systemic corticosteroids (of around five days) lead to worse outcomes than are seen with longer (10 to 14 d) courses.
Acute Exacerbations of COPD

- Definition:
  - Sustained (>24-48 h) worsening of dyspnea, cough, or sputum production leading to an increased use of medications

- Etiology:
  - Viral URTI, bacteria, air pollution, CHF, PE, MI must be considered

- Management:
  - ABCs, consider assisted ventilation if decreasing LOC or poor ABGs
  - O₂: target 88-92% SaO₂ for CO₂ retainers
  - Bronchodilators by MDI with spacer or nebulizer
  - SABA + anticholinergic, e.g. salbutamol and ipratropium bromide via nebulizers x 3 back-to-back q15min
  - Systemic corticosteroids: IV dexamethasone or oral prednisone
  - Antibiotics for exacerbations with increased sputum production and at least one of the following: increased dyspnea or sputum purulence
  - Simple exacerbation (no risk factors): amoxicillin, 2nd or 3rd generation cephalosporin, macrolide, or TMP-SMX
  - Complicated exacerbation (one of: FEV₁ ≤50% predicted, ≥4 exacerbations per year, ischemic heart disease, home O₂ use, chronic oral steroid use): fluoroquinolone or β-lactam + β-lactamase inhibitor (amoxicillin/clavulanate)
  - Post exacerbation: rehabilitation with general conditioning to improve exercise tolerance

- ICU Admission
  - For life threatening exacerbations
  - Ventilatory support
  - Non-invasive: NPPV, BiPAP
  - Conventional mechanical ventilation

Prognosis in COPD

- Prognostic factors
  - Level of dyspnea is the single best predictor
  - Development of complications, e.g. hypoxemia or cor pulmonale
  - 5 yr survival
    - FEV₁ <1 L = 50%
    - FEV₁ <0.75 L = 33%
  - BODE index for risk of death in COPD
    - Greater score = higher probability the patient will die from COPD; score can also be used to predict hospitalization
  - 10 point index consisting of four factors
    - Body mass index (BMI): <21 (+1 point)
    - Obstruction (FEV₁): 50-64% (+1), 36-49% (+2), <35% (+3)
    - Dyspnea (MRC scale): walks slower than people of same age on level surface, stops occasionally (+1), stops at 100 yards or a few minutes on the level (+2), too breathless to leave house or breathless when dressing/undressing (+3)
    - Exercise capacity (6 minute walk distance): 250-349 m (+1), 150-249 m (+2), <149 m (+3)

COPD Stage

- Mild
- Moderate
- Severe

MRC Dyspnea Scale

- II
- V

Education/Self-management (smoking cessation and exercise)

PRN short-acting bronchodilators

Inhaled corticosteroids (ICS)/LABA

Rehabilitation

Surgery

Systemic Corticosteroids for Acute Exacerbations of Chronic Obstructive Pulmonary Disease

**Diagnosis:**

- Acute exacerbations of COPD (AECOPD)

**Intervention:**

- Oral or parenteral corticosteroids vs. placebo

**Outcome:**

- Treatment failure, risk of relapse, time to next COPD exacerbation, likelihood of adverse event, length of hospital stay, and lung function at end of treatment

**Results:**

- Systemic corticosteroids reduced the risk of treatment failure by over half compared with placebo in nine studies (n = 917) with median treatment duration 14 d, odds ratio (OR) 0.49 (95% CI 0.35-0.67). The evidence was graded as high quality and it would have been necessary to treat nine people (95% CI 7.1-14) with systemic corticosteroids to avoid one treatment failure. There was moderate-quality evidence for a lower rate of relapse by one month for treatment with systemic corticosteroid in two studies (n = 415) (hazard ratio [HR] 0.78; 95% CI 0.63-0.97). Mortality up to 30 d was not reduced by treatment with systemic corticosteroids compared with control in 12 studies (n = 1,319; OR 1.00; 95% CI 0.60-1.66). FEV₁ measured up to 72 h, showed significant treatment benefits (1 studies; n = 849; mean difference [MD] 140 mL, 95% CI 100-180); however, this benefit was not observed at later time points. The likelihood of adverse events increased with corticosteroid treatment (OR 2.33; 95% CI 1.99-3.64). The risk of hyperglycemia was significantly increased (OR 2.97; 95% CI 1.66-4.19). For general hospital treatment, duration of hospitalization was significantly shorter with corticosteroid treatment (MD -1.22 d; 95% CI -2.26 to -0.18), with no significant difference in the duration of inpatient treatment, duration of hospitalization was significantly shorter with corticosteroid treatment (MD -1.22 d; 95% CI -2.26 to -0.18), with no difference in length of stay in the intensive care unit (ICU) setting. Comparison of parenteral versus oral treatment showed no significant difference in the primary outcomes of treatment failure, relapse or mortality or for any secondary outcomes.

**Conclusion:**

- There is high-quality evidence to support treatment of exacerbations of COPD with systemic corticosteroids by the oral or parenteral route in reducing the likelihood of treatment failure and relapse by 1 mo. Shortening length of stay in hospital inpatients not requiring assisted ventilation in ICU and giving earlier improvement in lung function and symptoms. There is no evidence of benefit for parenteral treatment compared with oral treatment with corticosteroid on treatment failure, relapse or mortality. There is an increase in adverse drug effects with corticosteroid treatment, which is greater with parenteral administration compared with oral treatment.
## Bronchiectasis

### Definition
- irreversible dilatation of airways due to inflammatory destruction of airway walls resulting from persistently infected mucus
- usually affects medium sized airways
- *P. aeruginosa* is the most common pathogen; *S. aureus, H. influenzae*, and nontuberculous mycobacteria also common

### Table 16. Etiology and Pathophysiology of Bronchiectasis

<table>
<thead>
<tr>
<th>Obstruction</th>
<th>Post-Infectious (results in dilatation of bronchial walls)</th>
<th>Impaired Defenses (leads to interference of drainage, chronic infections, and inflammation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumour</td>
<td>Pneumonia</td>
<td>Hypogammaglobulinemia</td>
</tr>
<tr>
<td>Foreign body</td>
<td>TB</td>
<td>CF</td>
</tr>
<tr>
<td>Thick mucus</td>
<td>Measles</td>
<td>Defective leukocyte function</td>
</tr>
<tr>
<td></td>
<td>Pertussis</td>
<td>Ciliary dysfunction (Kartagener’s syndrome: bronchiectasis, sinusitis, situs inversus)</td>
</tr>
<tr>
<td></td>
<td>Allergic bronchopulmonary aspergillosis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>MAC</td>
<td></td>
</tr>
</tbody>
</table>

### Signs and Symptoms
- chronic cough, purulent sputum (but 10-20% have dry cough), hemoptysis (can be massive), recurrent pneumonia, local crackles (inspiratory and expiratory), wheezes
- clubbing
- may be difficult to differentiate from chronic bronchitis

### Investigations
- PFTs: often demonstrate obstructive pattern but may be normal
- CXR
  - nonspecific: increased markings, linear atelectasis, loss of volume in affected areas
  - specific: “tram tracking” – parallel narrow lines radiating from hilum, cystic spaces, honeycomb like structures
- high-resolution thoracic CT (diagnostic, gold standard)
  - 87-97% sensitivity, 93-100% specificity
  - “signet ring”: dilated bronchi with thickened walls where diameter bronchus > diameter of accompanying artery
- sputum cultures (routine + AFB)
- serum Ig levels
- sweat chloride if cystic fibrosis suspected (upper zone predominant)

### Treatment
- vaccination: influenza and Pneumovax®
- antibiotics (oral, IV, inhaled): routinely used for mild exacerbations, driven by sputum sensitivity; macrolides may be used chronically for an anti-inflammatory effect
- inhaled antibiotics (tobramycin) used chronically to suppress pseudomonas and reduce exacerbations
- inhaled corticosteroids: decrease inflammation and improve FEV₁
- oral corticosteroids for acute, major exacerbations
- chest physiotherapy, breathing exercises, physical exercise
- pulmonary resection: in selected cases with focal bronchiectasis

## Cystic Fibrosis

- see *Pediatrics*, P90

### Pathophysiology
- chloride transport dysfunction: thick secretions from exocrine glands (lung, pancreas, skin, reproductive organs) and blockage of secretory ducts

### Clinical Features
- results in severe lung disease, pancreatic insufficiency, diabetes, and azoospermia
- other manifestations: meconium ileus in infancy, distal ileal obstruction in adults, sinusitis, liver disease
- chronic lung infections
  - *S. aureus*: early
  - *P. aeruginosa*: most common
  - *B. cepacia*: worse prognosis but less common
  - *Aspergillus fumigatus*

### Investigations
- sweat chloride test
  - increased concentrations of NaCl and K⁺ ([Cl⁻] >60 mmol/L is diagnostic in children)
- heterozygotes have normal sweat tests (and no symptoms)
• PFTs
  - early: airflow limitation in small airways
  - late: severe airflow obstruction, hyperinflation, gas trapping, decreased DL_{CO} (very late)
• ABGs
  - hypoxemia, hypercapnia later in disease with eventual respiratory failure and cor pulmonale
• CXR
  - hyperinflation, increased pulmonary markings (especially upper lobes)

Treatment
- chest physiotherapy and postural drainage
- bronchodilators (salbutamol ± ipratropium bromide)
- inhaled mucolytic (reduces mucus viscosity), hypertonic saline DNase
- inhaled tobramycin
- lung transplant
- pancreatic enzyme replacements

Prognosis
- depends on: infections (cepacia colonization), FEV₁, acute pulmonary exacerbations, lung transplant vs. non-lung transplant

Interstitial Lung Disease

Definition
- a group of disorders which cause progressive scarring of lung tissue
- this scarring can eventually impair lung function and gas exchange

Pathophysiology
- inflammatory and/or fibrosing process in the alveolar walls → distortion and destruction of normal alveoli and microvasculature
- typically associated with
  - lung restriction (decrease in TLC and VC)
  - decreased lung compliance (increased or normal FEV₁/FVC)
  - impaired diffusion (decreased DL_{CO})
  - hypoxemia due to V/Q mismatch (usually without hypercapnia until end stage)
  - pulmonary HTN and cor pulmonale occur with advanced disease secondary to hypoxemia and blood vessel destruction

Etiology
- >100 known disorders can cause ILD
- majority due to unknown agents or cause

Table 17. Interstitial Lung Diseases

<table>
<thead>
<tr>
<th>UNKNOWN ETIOLOGY</th>
<th>KNOWN ETIOLOGY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Idiopathic interstitial pneumonias</td>
<td>Sarcoïdosis</td>
</tr>
<tr>
<td>UIP (usual interstitial pneumonia e.g. IPF)</td>
<td>Langerhans-cell histiocytosis (eosinophilic granuloma)</td>
</tr>
<tr>
<td>NSIP (non-specific interstitial pneumonia)</td>
<td>Lymphangioleiomyomatosis</td>
</tr>
<tr>
<td>UIP (lymphohytic interstitial pneumonia)</td>
<td></td>
</tr>
<tr>
<td>CIP (cryptogenic organizing pneumonia e.g. BOOP)</td>
<td></td>
</tr>
<tr>
<td>DIP (desquamative interstitial pneumonia)</td>
<td></td>
</tr>
<tr>
<td>IPPFE (idiopathic pleuroparenchymal fibroelastosis)</td>
<td></td>
</tr>
<tr>
<td>AFP (acute fibrous and organizing pneumonia)</td>
<td></td>
</tr>
</tbody>
</table>

In ILD think
FASSTEN and BAD RASH
Upper Lung Disease (FASSTEN)
- Farmer’s lung (hypersensitivity pneumonia)
- Ankylosing spondylitis
- Sarcoidosis
- Silicosis
- TB
- Eosinophilic granuloma (Langerhans-cell histiocytosis)
- Neurofibromatosis

Lower Lung Disease (BADRASH)
- Bronchiolitis obliterans with organizing pneumonia (BOOP)
- Asbestosis
- Drugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs)
- Rheumatologic disease
- Aspiration
- Scleroderma
- Hamman Rich (acute interstitial pneumonia) and IPF

ILD Associated with Systemic Rheumatic Disorders
- Scleroderma
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Polyomysitis/dermatomyositis
- Anti-synthetase syndromes
- Mixed connective tissue disease

Environment/Occupation Associated ILD
- Hypersensitivity pneumonitis (usually organic antigen)
- Farmer’s lung
- Air conditioner/humidifier lung
- Bird breeder’s lung
- Pneumoconioses (inorganic dust)
- Silicosis
- Asbestosis
- Coal worker’s pneumoconiosis
- Chronic beryllium disease
- Pneumonitis from gases/lumes/vapour

ILD Associated with Drugs or Treatments
- Antibiotics (nitrofurantoin)
- Anti-inflammatory agents (methotrexate)
- Cardiovascular drugs (amiodarone)
- Antineoplastic agents (chemotherapy agents)
- Illicit drugs
- Radiation

ILD Associated with Pulmonary Vasculitis
- Granulomatosis with Polyangiitis (GPA)
- Goodpasture’s syndrome
- Idiopathic pulmonary hemosiderosis

Inherited Disorders
- Familial IPF
- Telomerase mutations
- Neurofibromatosis
- Tuberculosis
- Gaucher’s disease

Alveolar Filling Disorders
- Chronic eosinophilic pneumonia
- Pulmonary alveolar proteinosis

FASSTEN: Farmer’s lung, ankylosing spondylitis, silicosis, tuberculosis, eosinophilic granuloma, lymphangioleiomyomatosis
BADRASH: Bronchiolitis obliterans with organizing pneumonia, asbestosis, drugs (nitrofurantoin, hydralazine, INH, amiodarone, many chemo drugs), rheumatologic disease, aspiration, scleroderma, Hamman Rich (acute interstitial pneumonia) and IPF
Signs and Symptoms

- dyspnea, especially on exertion
- nonproductive cough
- crackles (dry, fine, end-inspiratory)
- clubbing (especially in IPF and asbestosis)
- features of cor pulmonale
- note that signs and symptoms vary with underlying disease process
  • e.g. sarcoidosis is seldom associated with crackles and clubbing

Investigations

- CXR/high resolution CT (see Medical Imaging, MI7)
  • usually decreased lung volumes
  • reticular, nodular, or reticulonodular pattern (nodular <3 mm)
  • hilar/mediastinal adenopathy (especially in sarcoidosis)
- PFTs
  • restrictive pattern: decreased lung volumes and compliance
  • normal or increased FEV/FVC, e.g. flow rates are often normal or high when corrected for absolute lung volume
  • DLCO decreased due to V/Q mismatch (less surface area for gas exchange ± pulmonary vascular disease)
- ABGs
  • hypoxemia and respiratory alkalosis may be present with progression of disease
- other
  • bronchoscopy, bronchoalveolar lavage, lung biopsy
  • ESR, ANA (lupus), RF (RA), serum-precipitating antibodies to inhaled organic antigens (hypersensitivity pneumonitis), c-ANCA (GPA), anti-GBM (Goodpasture’s)

Unknown Etiologic Agents

IDIOPATHIC PULMONARY FIBROSIS

Definition

- also known as usual interstitial pneumonia or cryptogenic fibrosing alveolitis
- a progressive, irreversible condition characterized by fibrosis of lung parenchyma with no known cause
  • chest CT usually shows honeycomb lung, lung biopsy shows UIP (usual interstitial pneumonia) pattern
  • commonly presents over age 50, incidence rises with age; males > females
- DDx
  • other idiopathic interstitial pneumonia, especially NSIP, but also COP and
    • desquamative interstitial pneumonitis (DIP)
    • lymphocytic interstitial pneumonitis (LIP): usually 2nd to immune conditions such as HIV (mostly in children), Sjögren’s

Signs and Symptoms

- commonly presents over age 50, incidence rises with age; males > females
- dyspnea on exertion, nonproductive cough, constitutional symptoms, late inspiratory fine crackles at lung bases, clubbing

Investigations

- labs (nonspecific, autoimmune serology usually negative)
- CXR: reticular or reticulonodular pattern with lower lung predominance; may appreciate honeycombing in advanced disease
- high resolution CT: lower zone peripheral reticular markings, traction bronchiectasis, honeycombing; ground glass, consolidation, or nodules should not be prominent in IPF
- biopsy: rarely for UIP as honeycombing makes radiologic diagnosis possible

Treatment

- O₂
- N-acetylcysteine (anti-oxidant)
- pirfenidone and nintedanib may slow disease progression
- lung transplantation for advanced disease
- mean survival of 3-5 yr after diagnosis

SARCOIDOSIS

Definition

- idiopathic non-infectious granulomatous multi-system disease with lung involvement in 90%
- characterized pathologically by non-caseating granulomas
- numerous HLA antigens have been shown to play a role and familial sarcoidosis is now recognized
Epidemiology

• typically affects young and middle-aged patients
• higher incidence among African Americans and people at northern latitudes e.g. Scandinavia, Canada

Signs and Symptoms

• asymptomatic, cough, dyspnea, fever, arthralgia, malaise, erythema nodosum, chest pain
• chest exam often normal
• common extrapulmonary manifestations
  ▪ cardiac (arrhythmias, sudden death)
  ▪ eye involvement (anterior or posterior uveitis)
  ▪ skin involvement (skin papules, erythema nodosum, lupus pernio)
  ▪ peripheral lymphadenopathy
  ▪ arthralgia
  ▪ hepatomegaly ± splenomegaly
• less common extra-pulmonary manifestations involve bone, CNS, kidney
• two acute sarcoid syndromes
  ▪ Lofgren's syndrome: fever, erythema nodosum, bilateral hilar lymphadenopathy, arthralgias
  ▪ Heerfordt-Waldenstrom syndrome: fever, parotid enlargement, anterior uveitis, facial nerve palsy

Investigations

• CBC (cytopenias from spleen or marrow involvement)
• serum electrolytes, creatinine, liver enzymes, calcium (hypercalcemia/hypercalciuria due to vitamin D activation by granulomas)
• hypergammaglobulinemia, occasionally RF positive
• elevated serum ACE (non-specific and non-sensitive)
• CXR: predominantly nodular opacities especially in upper lung zones ± hilar adenopathy
• PFTs: normal, obstructive pattern, restrictive pattern with normal flow rates and decreased DLco, or mixed obstructive/restrictive pattern
• ECG: to rule out conduction abnormalities
• slit-lamp eye exam: to rule out uveitis

Diagnosis

• biopsy
  ▪ transbronchial lung biopsy, transbronchial lymph node aspiration, endobronchial ultrasound guided surgical (EBUS) biopsy, or mediastinoscopic lymph node biopsy for granulomas
  ▪ in ~75% of cases, transbronchial biopsy shows granulomas in the parenchyma even if the CXR is normal

Staging

• radiographic, based on CXR
  ▪ Stage 0: normal radiograph
  ▪ Stage I: bilateral hilar lymphadenopathy ± right paratracheal lymphadenopathy
  ▪ Stage II: bilateral hilar lymphadenopathy and diffuse interstitial disease
  ▪ Stage III: interstitial disease only (reticulonodular pattern or nodular pattern)
  ▪ Stage IV: pulmonary fibrosis (honeycombing)

Treatment

• 85% of stage I resolve spontaneously
• 50% of stage II resolve spontaneously
• steroids for symptoms, declining lung function, hypercalcemia, or involvement of eye, CNS, kidney, or heart (not for abnormal CXR alone)
• methotrexate or other immunosuppressives occasionally used

Prognosis

• approximately 10% mortality secondary to progressive fibrosis of lung parenchyma

Known Etiologic Agents

HYPERSENSITIVITY PNEUMONITIS

• also known as extrinsic allergic alveolitis
• non-IgE mediated inflammation of lung parenchyma (acute, subacute, and chronic forms)
• caused by sensitization to inhaled agents, usually organic dust
• pathology: airway-centered, poorly formed granulomas and lymphocytic inflammation
• exposure usually related to occupation or hobby
  ▪ Farmer's Lung (Thermophilic actinomycetes)
  ▪ Bird Breeder's/Bird Fancier's Lung (immune response to bird IgA)
  ▪ Humidifier Lung (Aureobasidium pullulans)
  ▪ Sauna Taker's Lung (Aureobasidium spp.)

Corticosteroids for Pulmonary Sarcoidosis

Cochrane DB Syst Rev 2005;CD001114
Study: Meta-analysis of 13 RCTs involving 1,986 participants examining the use of steroids (oral or inhaled) in sarcoidosis.
Results: Oral steroids demonstrated an improvement in CXR (RR 1.46, 95% CI 1.01-2.09). For inhaled corticosteroids, two studies showed no improvement in lung function and one study showed an improvement in diffusing capacity. No data on side-effects.
Conclusions: Oral steroids improve CXR findings and global scores of CXR, symptoms, and spirometry over 3-24 mo, but do not improve lung function or modify disease course. Oral steroids may be of benefit for patients with Stage 2 and 3 disease.
Signs and Symptoms
- acute presentation: (4-6 h after exposure)
  - dyspnea, cough, fever, chills, malaise (lasting 18-24 h)
  - CXR: diffuse infiltrates
- type III (immune complex) reaction
- subacute presentation: more insidious onset than acute presentation
- chronic presentation
  - insidious onset
  - dyspnea, cough, malaise, anorexia, weight loss
  - PFTs: progressively restrictive
- CXR: predominantly upper lobe reticulonodular pattern
- type IV (cell mediated, delayed hypersensitivity) reaction (see Rheumatology, RH2)
- in both acute and chronic reactions, serum precipitins may be detectable (neither sensitive nor specific)

Treatment
- early diagnosis: avoidance of further exposure is critical as chronic changes are irreversible
- systemic corticosteroids can relieve symptoms and speed resolution

PNEUMOCONIOSES
- reaction to inhaled inorganic dusts 0.5-5 µm in size
- no effective treatment, therefore key is exposure prevention through the use of protective equipment
- smoking cessation, annual influenza and pneumococcal vaccination, rehabilitation, lung transplant for endstage disease

Table 18. Pneumoconioses

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Etiology</th>
<th>Symptoms</th>
<th>Investigations</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silicosis</td>
<td>At risk population: sandblasters, rock miners, stone cutters, quarry and highway workers. Generally requires &gt;20 yr exposure; may develop with much shorter but heavier exposure.</td>
<td>Dyspnea, cough, and wheezing</td>
<td>CXR: upper &gt; lower lobe. Early: nodular disease (simple pneumoconiosis), lung function usually normal. Late: nodules coalesce into masses (progressive massive fibrosis). Possible hilar lymph node enlargement (frequently calcified), especially “egg shell” calcification.</td>
<td>Mycobacterial infection (e.g. TB).</td>
</tr>
<tr>
<td>Coal Worker's Pneumoconiosis (CWP)</td>
<td>At risk population: coal workers, graphite workers. Coal and silica, coal is less fibrogenic than silica.</td>
<td>Pathologic hallmark is coal macule. Simple CWP. No signs or symptoms, usually normal lung function. Complicated CWP (also known as progressive massive fibrosis). Dyspnea Course: few patients progress to complicated CWP.</td>
<td>Simple CWP. CXR: multiple nodular opacities, mostly upper lobe. Complicated CWP. CXR: opacities larger and coalesce.</td>
<td>Caplan’s syndrome: rheumatoid arthritis and CWP present as larger nodules.</td>
</tr>
</tbody>
</table>

INTERSTITIAL LUNG DISEASE ASSOCIATED WITH DRUGS OR TREATMENTS

Drug-Induced
- antineoplastic agents: bleomycin, mitomycin, busulfan, cyclophosphamide, methotrexate, chlorambucil, BCNU (carmustine)
- antibiotics: nitrofurantoin, penicillin, sulfonamide
- cardiovascular drugs: amiodarone, tocainide
- anti-inflammatory agents: methotrexate, penicillamine
- gold salts
- illicit drugs (heroin, methadone)
- rituximab, anti-TNF-α agents (infliximab, etanercept, adalimumab)

Radiation-Induced
- early pneumonitis: approximately 6 wk post-exposure
- late fibrosis: 6-12 mo post-exposure
- infiltrates conform to the shape of the radiation field
Pulmonary Vascular Disease

Pulmonary Hypertension

Definition
- mean pulmonary arterial pressure >25 mmHg at rest and >30 mmHg with exercise, or a systolic pulmonary artery pressure of >40 mmHg at rest
- in the past, pulmonary HTN was classified as primary or secondary pulmonary HTN, but this classification was modified to a more clinically useful, treatment based classification

Table 19. World Health Organization Classification of Pulmonary Hypertension

<table>
<thead>
<tr>
<th>Classification</th>
<th>Some Causes</th>
<th>Treatment Options</th>
<th>Consider in All Patients with PH</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Pulmonary Arterial HTN</td>
<td>Idiopathic, Collagen vascular disease (scleroderma, SLE, RA), Congenital systemic-to-pulmonary shunts (Eisenmenger syndrome), Portopulmonary HTN, HIV infection, Drugs and toxins (e.g. anorexigens), Pulmonary veno-occlusive disease, Schistosomiasis, Pulmonary capillary hemangiomatosis, Sickle cell disease</td>
<td>No effective treatment CCBs or advanced therapy often needed, The latter includes: prostanoids, endothelin receptor antagonists, PDE5 inhibitors, Lung transplantation</td>
<td>Oxygen therapy, Exercise, Consider anticoagulation</td>
</tr>
<tr>
<td>II. Pulmonary HTN due to Left Heart Disease</td>
<td>Left-sided atrial or ventricular heart disease (e.g. LV dysfunction), Left-sided valvular heart disease (e.g. aortic stenosis, mitral stenosis)</td>
<td>Treat underlying heart disease</td>
<td></td>
</tr>
<tr>
<td>III. Pulmonary HTN due to Lung Disease and/or Hypoxia</td>
<td>Parenchymal lung disease (COPD, interstitial fibrosis, cystic fibrosis), Chronic alveolar hypoxia (chronic high altitude, alveolar hypoventilation disorders, sleep-disordered breathing)</td>
<td>Treat underlying cause of hypoxia and correct with supplemental oxygen (proven mortality benefit)</td>
<td></td>
</tr>
<tr>
<td>IV. Chronic Thromboembolic Pulmonary HTN (CTEPH)</td>
<td>Thromboembolic obstruction of proximal pulmonary arteries, Obstruction of distal pulmonary arteries – PE (thrombus, foreign material, tumour, in situ thrombosis)</td>
<td>Anticoagulation, thromboendarterectomy</td>
<td></td>
</tr>
<tr>
<td>V. Pulmonary HTN with Unclear Multifactorial Mechanisms</td>
<td>Hematologic disorders, Systemic disorders (e.g. sarcoidosis), Metabolic disorders, Exttrinsic compression of central pulmonary veins (tumour, adenopathy, fibrosing mediastinitis)</td>
<td>Treat underlying cause</td>
<td></td>
</tr>
</tbody>
</table>


Mechanisms of Pulmonary Hypertension (simplified)
- hypoxic vasoconstriction
  - chronic hypoxia causes pulmonary vasoconstriction by a variety of actions on the pulmonary artery endothelium and smooth muscle cells, such as: down regulation of endothelial nitric oxide synthase and alteration of voltage gated potassium channels leading to vasoconstriction
  - causes: COPD, chronic alveolar hypoxia
- decreased area of pulmonary vascular bed
  - leads to a rise in resting pulmonary arterial pressure
  - causes: collagen vascular disease, HIV infection, drugs and toxins, thrombotic or embolic disease, inflammatory, pulmonary capillary hemangiomatosis, interstitial fibrosis, CF
- volume and pressure overload
  - significant HTN only occurs with excessive volume overload, since pulmonary artery pressure will not rise until pulmonary blood flow exceeds 2.5x the basal rate
  - causes: congenital systemic-to-pulmonary shunts (e.g. VSD, ASD, PDA), portopulmonary HTN, left-sided heart conditions, pulmonary veno-occlusive disease, extrinsic compression of central pulmonary veins

Pulmonary arterial pressures are measured by pulmonary artery catheters (i.e. Swan-Ganz catheter) which are inserted into a large vein (often internal jugular). A balloon at the end of the catheter tip is inflated causing the catheter to advance through the right side of the heart and into the pulmonary artery. This allows for the measurement of RA, RV, PA, and pulmonary capillary wedge pressures as well as sampling of mixed venous blood. A thermostor near the end of the catheter also allows for assessment of cardiac output by thermodilution
IDIOPATHIC PULMONARY ARTERIAL HYPERTENSION (PRIMARY PULMONARY HYPERTENSION)

Definition
- pulmonary HTN in the absence of a demonstrable cause
- exclude:
  - left-sided cardiac valvular disease
  - myocardial disease
  - congenital heart disease
  - any clinically significant parenchymal lung disease
  - systemic connective-tissue disease
  - chronic thromboembolic disease

Epidemiology
- usually presents in young females (20-40 yr); mean age of diagnosis is 36 yr
- most cases are sporadic; familial predisposition in 10% of cases, some linked to mutations in BMPR2
- may be associated with the use of anorexic drugs (e.g. Aminorex®, Fenfluramine*), amphetamines, and cocaine

Signs and Symptoms

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Loud, palpable P₂</td>
</tr>
<tr>
<td>Fatigue</td>
<td>RV heave</td>
</tr>
<tr>
<td>Retrosternal chest pain</td>
<td>Right-sided S₂ (due to RVH)</td>
</tr>
<tr>
<td>Syncope</td>
<td>Systolic murmur (tricuspid regurgitation [TR])</td>
</tr>
<tr>
<td>Symptoms of underlying disease</td>
<td>If RV failure: right sided S₂, increased JVP, positive HJR, peripheral edema, TR</td>
</tr>
<tr>
<td></td>
<td>Reynaud's phenomenon</td>
</tr>
</tbody>
</table>

Investigations
- CXR: enlarged central pulmonary arteries, cardiac changes due to RV enlargement (filling of retrosternal air space)
- ECG
  - RVH/right-sided strain (see Cardiology and Cardiac Surgery, C36)
- 2-D echo doppler assessment of right ventricular systolic pressure
- cardiac catheterization: direct measurement of pulmonary artery pressures (necessary to confirm diagnosis)
- PFTs to asses for underlying lung disease: DLCO usually reduced; volumes and flows normal
- CT angiogram to assess lung parenchyma and possible PE
- V/Q scan ± pulmonary angiogram to rule out thromboembolic disease
- serology: ANA positive in 30% of patients with primary pulmonary HTN; other serologic markers can be used in the appropriate clinical setting

Treatment
- see Table 19

Prognosis
- 2-3 yr mean survival from time of diagnosis
- survival decreases to approximately 1 yr if severe pulmonary HTN or right-heart failure

Pulmonary Embolism

Definition
- lodging of a blood clot in the pulmonary arterial tree with subsequent increase in pulmonary vascular resistance, impaired V/Q matching, and possibly reduced pulmonary blood flow

Etiology and Pathophysiology
- one of the most common causes of preventable death in the hospital
- proximal leg thrombi (popliteal, femoral, or iliac veins) are the source of most clinically recognized pulmonary emboli
- thrombi often start in calf, but must propagate into proximal veins to create a sufficiently large thrombus for a clinically significant PE
- fewer than 30% of patients have clinical evidence of DVT (e.g. leg swelling, pain, or tenderness)
- always suspect PE if patient develops fever, sudden dyspnea, chest pain, or collapse 1-2 wk after surgery

Guidelines for Vasodilator Response in Pulmonary Arterial HTN
- Patients with IPAH that respond to vasodilators acutely, have an improved survival with long-term use of CCBs
- Vasoreactivity testing: short-acting agent such as IV epoprostenol, IV adenosine, or inhaled NO
- Positive vasodilator response: mean PAP fall of at least 10 mm Hg to ≤40 mm Hg with an increased or unchanged cardiac output (European Society of Cardiology)
- Positive vasodilator response: should be considered as candidate for trial of oral CCB therapy

Medication Therapy for Pulmonary Arterial Hypertension. ACCP Evidence-Based Clinical Practice Guidelines. Chest 2004;126:35S-75S

Vircow's Triad
- Venous stasis
- Endothelial cell damage
- Hypercoagulable states

Multidetector Computed Tomography for Acute Pulmonary Embolism (PIOPED II Trial)
NEJM 2006;354:2317-2327
Study: Multicentre, prospective study investigating accuracy of computed tomography angiography (CTA alone and combined with venous phase imaging [CTA-CTV]) for the diagnosis of PE
Patients: 824 patients of several thousand eligible for study received reference diagnosis to confirm absence or presence of PE (V/Q scan, venous compression US of lower extremities, and pulmonary digital-subtraction angiography (DSA) if necessary). To confirm absence, patients in whom PE was excluded were telephoned 3-6 mo after enrollment. Any deaths were reviewed by an outcome committee. All patients enrolled also underwent clinical assessment of PE (including a Wells score) prior to imaging
Outcomes: Diagnosis of pulmonary embolism
Results: 773 of 824 patients had adequate CTA for interpretation. PE was diagnosed in 192 of the 824 patients. Sensitivity was 83% (150 of 181 patients; 95% CI 0.76-0.90) and specificity was 98% (567 of 592 patients; 95% CI 0.93-0.97). However, the predictive value of CTA-CTV varied when clinical pre-test probability was taken into account. PPV of CTA for high, intermediate and low clinical probability were 96% (95% CI 0.78-0.99), 92% (95% CI 0.84-0.98), and 54% (95% CI 0.40-0.70), respectively. NPV of CTA for high, intermediate and low clinical probability were 86% (95% CI 0.32-0.80), 89% (95% CI 0.82-0.93), and 96% (95% CI 0.82-0.98) respectively
Conclusion: CTA is effective for diagnosing or excluding PE in accordance with assessment of clinical pre-test probability. When clinical probability is inconsistent with imaging results, further investigations are required to rule out PE
Risk Factors
• stasis
  • immobilization: paralysis, stroke, bed rest, prolonged sitting during travel, immobilization of an extremity after fracture
• obesity, CHF
• chronic venous insufficiency
• endothelial cell damage
• post-operative injury, trauma
• hypercoagulable states
  • underlying malignancy (particularly adenocarcinoma)
  • cancer treatment (chemotherapy, hormonal)
  • exogenous estrogen administration (OCP, HRT)
• pregnancy, post-partum
• prior history of DVT/PE, family history
• nephrotic syndrome
  • coagulopathies: Factor V Leiden, Prothrombin 20210A variant, inherited deficiencies of antithrombin/protein C/protein S, antiphospholipid antibody, hyperhomocysteinemia, increased Factor VIII levels, and myeloproliferative disease
• increasing age

Investigations (if highly suspicious, go straight to CT angiogram)
• see Emergency Medicine, ER32

Table 21. Common Investigations for Pulmonary Embolism

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Purpose/Utility</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary Angiogram (Gold Standard)</td>
<td>Filling defect indicative of embolus; negative angiogram excludes clinically relevant PE</td>
</tr>
<tr>
<td>D-Dimer</td>
<td>Highly sensitive D-dimer result can exclude DVT/PE if pretest probability is already low</td>
</tr>
<tr>
<td>CT Angiogram</td>
<td>Both sensitive and specific for PE</td>
</tr>
<tr>
<td>Venous Duplex U/S or Doppler</td>
<td>With leg symptoms</td>
</tr>
<tr>
<td>ECG</td>
<td>Findings not sensitive or specific</td>
</tr>
<tr>
<td>CXR</td>
<td>Frequently normal; no specific features</td>
</tr>
<tr>
<td>V/Q Scan</td>
<td>Very sensitive but low specificity</td>
</tr>
<tr>
<td>Echocardiogram</td>
<td>Useful to assess massive or chronic PE</td>
</tr>
<tr>
<td>ABG</td>
<td>No diagnostic use in PE (insensitive and nonspecific)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Clinical Prediction Rule for Pulmonary Embolism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Probability</strong></td>
</tr>
<tr>
<td>Low (0–2)</td>
</tr>
<tr>
<td>Intermediate (3–6)</td>
</tr>
<tr>
<td>High (&gt;6)</td>
</tr>
</tbody>
</table>

D-dimer is elevated in patients with recent surgery, cancer, inflammation, infection, and severe renal dysfunction. It has good sensitivity and negative predictive value, but poor specificity and positive predictive value.

Evaluation of a Suspected Pulmonary Embolism
Low clinical probability of embolism

\[
\text{D-dimer (–ve) \rightarrow CT scan (–ve) \rightarrow ruled out (–ve)} \rightarrow \text{ruled out (–ve)} \\
\text{Intermediate or high probability} \\
\text{CT scan (+ve) \rightarrow ruled out (+ve) \rightarrow ruled in (+ve)} \rightarrow \text{ruled in (+ve)} \\
\]

Notes
• Use D-dimers only if low clinical probability, otherwise, go straight to CT.
• If using V/Q scans (CT contrast allergy or renal failure):
  • Negative V/Q scan rules out the diagnosis
  • High probability V/Q scan only rules in the diagnosis if high clinical suspicion
  • Inconclusive V/Q scan requires leg U/S to look for DVT or CT.
Treatment
- admit for observation (patients with DVT only are often sent home on LMWH)
- oxygen: supplemental O₂ if hypoxic or short of breath
- pain relief: analgesics if chest pain – narcotics or acetaminophen
- acute anticoagulation: therapeutic-dose SC LMWH or IV heparin – start ASAP
  - anticoagulation stops clot propagation, prevents new clots and allows endogenous fibrinolytic system to dissolve existing thromboemboli over months
- get baseline CBC, INR, aPTT ± renal function ± liver function
- for SC LMWH: dalteparin 200 U/kg once daily, enoxaparin 1 mg/kg bid or 1.5mg/kg once daily, or tinzaparin 175 U/kg once daily – no lab monitoring – avoid or reduce dose in renal dysfunction
- for IV heparin: bolus of 75 U/kg (usually 5,000 U) followed by infusion starting at 20 U/kg/h – aim for aPTT 2-3x control
- long-term anticoagulation
  - warfarin: start the same day as LMWH/heparin – overlap warfarin with LMWH/heparin for at least 5 d and until INR in target range of 2-3 for at least 2 d
  - LMWH instead of warfarin for pregnancy, active cancer, or high bleeding risk patients
  - direct thrombin inhibitors: can treat from outset with rivaroxaban; dabigatran has been shown to have lower bleeding risk than warfarin; no monitoring required, however agents not reversible, so avoid if bleeding concerns
- IV thrombolytic therapy
  - if patient has massive PE (hypotension or clinical right heart failure) and no contraindications
  - hastens resolution of PE but may not improve survival or long-term outcome and doubles risk of major bleeding
- interventional thrombolytic therapy
  - massive PE is preferentially treated with catheter-directed thrombolysis by an interventional radiologist
  - works better than IV thrombolytic therapy and fewer contraindications
- IVC filter: only if recent proximal DVT + absolute contraindication to anticoagulation
- duration of long-term anticoagulation: individualized, however generally
  - if reversible cause for PE (surgery, injury, pregnancy, etc.): 3-6 mo
  - if PE unprovoked: 6 mo to indefinite
  - if ongoing major risk factor (active cancer, antiphospholipid antibody, etc.): indefinite

Thromboprophylaxis
- mandatory for most hospital patients: reduces DVT, PE, all-cause mortality, cost-effective
- start ASAP
- continue at least until discharge or recommend extending for 35 d post-operatively, if major orthopedic surgery

Table 22. VTE Risk Categories and Prophylaxis (see Hematology, H35)

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Prophylaxis Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Thrombosis Risk</td>
<td>No specific prophylaxis</td>
</tr>
<tr>
<td>Medical patients: fully mobile Surgery: &lt; 30 min, fully mobile</td>
<td>Frequent ambulation</td>
</tr>
<tr>
<td>Moderate Thrombosis Risk</td>
<td>LMWH</td>
</tr>
<tr>
<td>Most general, gynecologic, urologic surgery</td>
<td>Low dose unfractionated heparin</td>
</tr>
<tr>
<td>Sick medical patients</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>High Thrombosis Risk</td>
<td>LMWH</td>
</tr>
<tr>
<td>Arthroplasty, hip fracture surgery</td>
<td>Fondaparinux</td>
</tr>
<tr>
<td>Major trauma, spinal cord injury</td>
<td>Fondaparinux (INR 2-3)</td>
</tr>
<tr>
<td>High Bleeding Risk</td>
<td>TED stockings, pneumatic compression devices</td>
</tr>
<tr>
<td>Neurosurgery, intracranial bleed</td>
<td>LMWH or low dose heparin when bleeding risk decreases</td>
</tr>
</tbody>
</table>

PE Rule Out Criteria (PERC)
Prospective Multicentre Evaluation of the Pulmonary Embolism Rule Out Criteria
J Thorac Oncol 2009;6:172
- Age less than 50 yr
- Heart rate less than 100 bpm
- Oxyhemoglobin saturation ≥95 percent
- No hemoptysis
- No estrogen use
- No prior DVT or PE
- No unilateral leg swelling
- No surgery or trauma requiring hospitalization within the past 4 wk

Acute PE can probably be excluded without further diagnostic testing if the patient meets all PERC criteria AND there is a low clinical suspicion for PE, according to either the Wells’ criteria or a low gestalt probability determined by the clinician prior to diagnostic testing for PE.

Extended Use of Dabigatran, Warfarin or Placebo in Venous Thromboembolism
NEJM 2013;368:709-718
Study: Two double blind, RCTs; one comparing against placebo, the other against active treatment.
Population: 4,199 patients (2,856 in active-control study, 1,343 in placebo-control study) with VTE who had completed at least 3 mo of therapy.
Intervention: In the active-control study, patients randomized to either 150 mg dabigatran or warfarin (INR 2.0-3.0). Patients in the placebo-control study received either 100 mg dabigatran or placebo.
Outcome: Recurrence of VTE, risk of major or clinically relevant bleed.
Results: In the active-control study, there was a hazard ratio (HR) of 1.14 (95% CI 0.79-1.64 for non-inferiority) of recurrent VTE with dabigatran vs. warfarin. HR of major or clinically relevant bleed was 0.94 (95% CI 0.47-1.81). In the placebo-control study, the HR of VTE with dabigatran vs. placebo was 0.09 (95% CI 0.02-0.25). HR of major or clinically relevant bleed was 2.92 (95% CI 1.53-5.60).
Conclusions: Dabigatran appears to be non-inferior to warfarin in the prevention of VTE recurrence. Dabigatran is associated with a lower risk of major or clinically relevant bleed than warfarin, but greater than placebo.

Malignancy Workup: 12% of patients with idiopathic VTE will have a malignancy.

The Use of Unfractionated Heparin Should Be Limited to:
- Patients with severe renal dysfunction (CrCl < 30 ml/min) in whom LMWH and novel oral anticoagulation should be avoided
- Patients at elevated risk of bleeding that may need rapid reversal of anticoagulation
- Patients who receive thrombolytic therapy
Table 23. Pulmonary Vasculitis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Definition</th>
<th>Pulmonary Features</th>
<th>Extra-pulmonary Features</th>
<th>Investigations</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulomatosis with Polyangiitis (Wegener’s Granulomatosis)</td>
<td>Systemic vasculitis of medium and small arteries</td>
<td>Necrotizing granulomatous lesions of the upper and lower respiratory tract</td>
<td>Focal necrotizing lesions of arteries and veins; crescentic glomerulonephritis</td>
<td>CXR: nodules, cavities, and alveolar opacities c-ANCA Tissue confirmation</td>
<td>Corticosteroids and cyclophosphamide or rituximab</td>
</tr>
<tr>
<td>Churg-Strauss Syndrome (eosinophilic granulomatosis with polyangiitis)</td>
<td>Multisystem disorder characterized by allergic rhinitis, asthma, and prominent peripheral eosinophilia</td>
<td>Asthma Infiltrates</td>
<td>Life-threatening systemic vasculitis involving the lungs, pericardium and heart, kidneys, skin, and PNS (mononeuritis multiplex)</td>
<td>Peripheral eosinophilia is the most common finding p-ANCA may be positive Biopsy involved tissue</td>
<td>Corticosteroids</td>
</tr>
<tr>
<td>Goodpasture’s Disease (see Nephrology, NP23)</td>
<td>A disorder characterized by diffuse alveolar hemorrhage and glomerulonephritis caused by anti-GBM antibodies, which cross-react with basement membranes of the kidney and lung</td>
<td>Hemoptysis May follow an influenza infection</td>
<td>Anemia</td>
<td>CXR: may see alveolar infiltrates if hemorrhage is profuse ELISA test with anti-GBM antibodies Renal biopsy/indirect immunofluorescence shows linear staining</td>
<td>Acutely: corticosteroids, plasmapheresis Immunosuppressive therapy Severe cases: bilateral nephrectomy</td>
</tr>
</tbody>
</table>

Goodpasture’s Disease is the most common collagen vascular disease affecting the lung

Differential of an Anterior Compartment Mass
- 4 Ts
  - Thymoma
  - Thyroid enlargement (goitre)
  - Teratoma
  - Tumours (lymphoma, parathyroid, esophageal, angiomaticus)

Mediastinal Components
- Anterior: sternum to pericardium and great vessels. Includes: thymus, extrapericardial aorta and branches, great veins, lymphatic tissues
- Middle: pericardium (anteriorly), posterior pericardial reflection, diaphragm, thoracic inlet. Includes: heart, intrapericardial great vessels, pericardium, trachea
- Posterior: posterior pericardial reflection, posterior border of vertebral bodies, first rib to the diaphragm. Includes: esophageus, vagus nerve, thoracic duct, sympathetic chain,azygos venous system

Horners Syndrome
Ptosis, Miosis, Anhydrosis

Scleroderma is the most common collagen vascular disease affecting the lung

Diseases of the Mediastinum and Pleura

Mediastinal Masses

Definition
- mediastinum: bound by the thoracic inlet, diaphragm, sternum, vertebral bodies, and the pleura
- can be broken down into 3 compartments: anterior, middle, and posterior

Etiology and Pathophysiology
- diagnosis is aided by location and patient’s age
- anterior compartment: more likely to be malignant
  - “Four Ts” (see sidebar), lymphoma, lipoma, pericardial cyst
- middle compartment
  - pericardial cyst, bronchogenic cyst/tumour, lymphoma, lymph node enlargement, aortic aneurysm
- posterior compartment
  - neurogenic tumours, meningocele, enteric cysts, lymphoma, diaphragmatic hernias, esophageal tumour, aortic aneurysm

Signs and Symptoms
- 50% asymptomatic (mainly benign); when symptomatic, 50% are malignant
- chest pain, cough, dyspnea, recurrent respiratory infections
- hoarseness, dysphagia, Horner’s syndrome, facial/upper extremity edema (SVC compression)
- paraneoplastic syndromes (e.g. myasthenia gravis [thymomas])

Investigations
- CXR (compare to previous)
- CT with contrast (anatomic location, density, relation to mediastinal vascular structures)
- MRI: specifically indicated in the evaluation of neurogenic tumours
- U/S (best for assessment of structures in close proximity to the heart and pericardium)
- radionuclide scanning: 131I (for thyroid), gallium (for lymphoma)
- biochemical studies: thyroid function, serum calcium, phosphate, PTH, AFP, ß-hCG
- biopsy (mediastinoscopy, percutaneous needle aspiration)
Management
• excision if symptomatic enlarging benign masses or concerns of malignancy
• resect bronchogenic cysts and localized neurogenic tumours via minimally invasive video assisted procedures
• exploration via sternotomy or thoracotomy
• diagnostic biopsy rather than major operation if mass is likely to be a lymphoma, germ cell tumour, or unresectable invasive malignancy
• ± post-operative radiotherapy/chemotherapy if malignant

Mediastinitis
• most common causes: post-operative complications of cardiovascular or thoracic surgical procedures

Acute
• etiology
  ▪ complication of endoscopy (e.g. esophageal perforation providing entry point for infection)
  ▪ esophageal or cardiac surgery
  ▪ tumour necrosis
• signs and symptoms
  ▪ fever, substernal pain
  ▪ pneumomediastinum, mediastinal compression
  ▪ Hamman's sign (auscultatory “crunch” during cardiac systole)
• treatment
  ▪ antibiotics, drainage, ± surgical closure of perforation

Chronic
• usually granulomatous process or fibrosis related to previous infection (e.g. histoplasmosis, TB, sarcoidosis, syphilis)

Pleural Effusions
Definition
• excess amount of fluid in the pleural space (normally up to 25 mL)

Etiology
• disruption of normal equilibrium between pleural fluid formation/entry and pleural fluid absorption/exit
• pleural effusions are classified as transudative or exudative
  ▪ distinguish clinically using Light's Criteria, which has a sensitivity of 98% and specificity of 83% for identifying exudative pleural effusions

Table 24. Laboratory Values in Transudative and Exudative Pleural Effusion

<table>
<thead>
<tr>
<th>Light's Criteria</th>
<th>Modified Light's Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein – Pleural/Serum</td>
<td>&gt;0.5</td>
</tr>
<tr>
<td>LDH – Pleural/Serum</td>
<td>&gt;0.6</td>
</tr>
<tr>
<td>Pleural LDH</td>
<td>&gt;2/3 upper limit of N serum LDH</td>
</tr>
</tbody>
</table>

Exudate = at Least One Criterion Met

Transudative Pleural Effusions
• pathophysiology: alteration of systemic factors that affect the formation and absorption of pleural fluid (e.g. increased capillary hydrostatic pressure, decreased plasma oncotic pressure)
• etiology
  ▪ CHF: usually right-sided or bilateral cirrhosis
  ▪ nephrotic syndrome, protein losing enteropathy, cirrhosis
  ▪ pulmonary embolism (may cause transudative but more often causes exudative effusion)
  ▪ peritoneal dialysis, hypothyroidism, CF, urinothorax

Exudative Pleural Effusions
• pathophysiology: increased permeability of pleural capillaries or lymphatic dysfunction
• etiology (see Table 25)
Table 25. Exudative Pleural Effusion Etiologies

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td>Parapneumonic effusion (associated with bacterial pneumonia, lung abscess)</td>
</tr>
<tr>
<td></td>
<td>Empyema (bacterial, fungal, TB)</td>
</tr>
<tr>
<td></td>
<td>TB pleuritis</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Lung carcinoma (35%)</td>
</tr>
<tr>
<td></td>
<td>Lymphoma (10%)</td>
</tr>
<tr>
<td></td>
<td>Metastases: breast (25%), ovary, kidney</td>
</tr>
<tr>
<td></td>
<td>Mesothelioma</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Collagen vascular diseases: RA, SLE</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td></td>
<td>Post-CABG</td>
</tr>
<tr>
<td></td>
<td>Drug reaction</td>
</tr>
<tr>
<td>Intra-Abdominal</td>
<td>Subphrenic abscess</td>
</tr>
<tr>
<td></td>
<td>Pancreatic disease (elevated pleural fluid amylase)</td>
</tr>
<tr>
<td></td>
<td>Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)</td>
</tr>
<tr>
<td>Intra-Thoracic</td>
<td>Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space due to trauma, tumour</td>
</tr>
<tr>
<td></td>
<td>Hemothorax: rupture of a blood vessel, commonly by trauma or tumours</td>
</tr>
<tr>
<td></td>
<td>Pneumothorax (spontaneous, traumatic, tension)</td>
</tr>
</tbody>
</table>

Other causes:

- Collagen vascular diseases: RA, SLE, PAN, Sjögren's syndrome, systemic lupus erythematosus
- Pulmonary embolism
- Post-CABG
- Drug reaction
- Intra-Abdominal:
  - Subphrenic abscess
  - Pancreatic disease (elevated pleural fluid amylase)
  - Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)
- Intra-Thoracic:
  - Esophageal perforation (elevated fluid amylase)
- Trauma
  - Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space due to trauma, tumour
  - Hemothorax: rupture of a blood vessel, commonly by trauma or tumours
  - Pneumothorax (spontaneous, traumatic, tension)
- Malignancy:
  - Lung carcinoma (35%)
  - Lymphoma (10%)
  - Metastases: breast (25%), ovary, kidney
  - Mesothelioma
- Inflammatory:
  - Collagen vascular diseases: RA, SLE
  - Pulmonary embolism
  - Post-CABG
  - Drug reaction
- Intra-Abdominal:
  - Subphrenic abscess
  - Pancreatic disease (elevated pleural fluid amylase)
  - Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)
- Intra-Thoracic:
  - Esophageal perforation (elevated fluid amylase)
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  - Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space due to trauma, tumour
  - Hemothorax: rupture of a blood vessel, commonly by trauma or tumours
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  - Mesothelioma
- Inflammatory:
  - Collagen vascular diseases: RA, SLE
  - Pulmonary embolism
  - Post-CABG
  - Drug reaction
- Intra-Abdominal:
  - Subphrenic abscess
  - Pancreatic disease (elevated pleural fluid amylase)
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- Intra-Thoracic:
  - Esophageal perforation (elevated fluid amylase)
- Trauma
  - Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space due to trauma, tumour
  - Hemothorax: rupture of a blood vessel, commonly by trauma or tumours
  - Pneumothorax (spontaneous, traumatic, tension)
- Malignancy:
  - Lung carcinoma (35%)
  - Lymphoma (10%)
  - Metastases: breast (25%), ovary, kidney
  - Mesothelioma
- Inflammatory:
  - Collagen vascular diseases: RA, SLE
  - Pulmonary embolism
  - Post-CABG
  - Drug reaction
- Intra-Abdominal:
  - Subphrenic abscess
  - Pancreatic disease (elevated pleural fluid amylase)
  - Meigs' syndrome (ascites and hydrothorax associated with an ovarian fibroma or other pelvic tumour)
- Intra-Thoracic:
  - Esophageal perforation (elevated fluid amylase)
- Trauma
  - Chylothorax: thoracic duct disrupted and chyle accumulates in the pleural space due to trauma, tumour
  - Hemothorax: rupture of a blood vessel, commonly by trauma or tumours
  - Pneumothorax (spontaneous, traumatic, tension)

Signs and Symptoms

- Often asymptomatic
- Dyspnea: varies with size of effusion and underlying lung function
- Pleuritic chest pain
- Inspection: trachea deviates away from effusion, ipsilateral decreased expansion
- Percussion: decreased tactile fremitus, dullness
- Auscultation: decreased breath sounds, bronchial breathing and egophony at upper level, pleural friction rub

Investigations

- **CXR**
  - Must have >200 mL of pleural fluid for visualization on PA film
  - Lateral: >50 mL leads to blunting of posterior costophrenic angle
  - Dense opacification of lung fields with concave meniscus
  - Decubitus: fluid will shift unless it is loculated
  - Supine: fluid will appear as general haziness
- **CT may be helpful in differentiating parenchymal from pleural abnormalities, may identify underlying lung pathology**
- **U/S** detects small effusions and can guide thoracentesis
- **Thoracentesis is indicated if pleural effusion is a new finding; be sure to send off blood work (LDH, glucose, protein) at the same time for comparison**
  - Risk of re-expansion pulmonary edema if >1.5 L of fluid is removed
  - Inspect for colour, character, and odour of fluid
  - Analyze fluid
- **pleural biopsy**: indicated if suspect TB, mesothelioma, or other malignancy (and if cytology negative)
- ± U/S: detects small effusions and can guide thoracentesis
- **Treatment depends on cause, ± drainage if symptomatic**
- **CT can be helpful in differentiating parenchymal from pleural abnormalities**

Table 26. Analysis of Pleural Effusion

<table>
<thead>
<tr>
<th>Measure</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Protein, LDH</td>
<td>Transudate vs. exudate</td>
</tr>
<tr>
<td>Gram stain, Ziehl-Nielsen stain (TB), culture</td>
<td>Looking for specific organisms</td>
</tr>
<tr>
<td>Cell count differential</td>
<td>Neutrophils vs. lymphocytes (lymphocytic effusion in TB, cancer, lymphoma, serositis)</td>
</tr>
<tr>
<td>Cytology</td>
<td>Malignancy, infection</td>
</tr>
<tr>
<td>Glucose (low)</td>
<td>RA, TB, empyema, malignancy, esophageal rupture</td>
</tr>
<tr>
<td>Rheumatoid factor, ANA, complement</td>
<td>Collagen vascular disease</td>
</tr>
<tr>
<td>Amylase</td>
<td>Pancreatitis, esophageal perforation, malignancy</td>
</tr>
<tr>
<td>pH</td>
<td>Empyema &lt; 7.2, TB, and mesothelioma &lt; 7.3</td>
</tr>
<tr>
<td>Blood</td>
<td>Mostly traumatic, malignancy, PE with infection, TB</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>Chylothorax from thoracic duct leakage, mostly due to trauma, lung CA, or lymphoma</td>
</tr>
</tbody>
</table>
Treatment
- thoracentesis
- treat underlying cause
- consider indwelling pleural catheter or pleurodesis in refractory effusions

Complicated Parapneumonic Effusion
- persistent bacteria in the pleural space but fluid is non-purulent
- neutrophils, pleural fluid acidosis (pH < 7.00), and high LDH
- often no bacteria grown since rapidly cleared from pleural space
- fibrin layer leading to loculation of pleural fluid
- treatment: antibiotics and drainage, treat as an empyema

Empyema

Definition
- pus in pleural space or an effusion with organisms seen on a Gram stain or culture (e.g. pleural fluid is grossly purulent)
- positive culture is not required for diagnosis

Etiology
- contiguous spread from lung infection (most commonly anaerobes) or infection through chest wall (e.g. trauma, surgery)

Signs and Symptoms
- fever, pleuritic chest pain

Investigations
- CT chest
- thoracentesis
- PMNs (lymphocytes in TB) ± visible organisms on Gram stain

Treatment
- antibiotic therapy for at least 4-6 wk (rarely effective alone)
- complete pleural drainage with chest tube
- if loculated, more difficult to drain – may require surgical drainage with video-assisted thoroscopic surgery (VATS), or surgical removal of fibrin coating to allow lung re-expansion (decortication)

Atelectasis
- see General Surgery, GS10

Pneumothorax

Definition
- presence of air in the pleural space

Pathophysiology
- entry of air into pleural space raises intrapleural pressure causing partial lung deflation

Etiology
- traumatic: penetrating or non-penetrating chest injuries
- iatrogenic (central venous catheter, thoracentesis, mechanical ventilation with barotrauma)
- spontaneous (no history of trauma)
  - primary (no underlying lung disease)
    - spontaneous rupture of apical subpleural bleb of lung into pleural space
    - predominantly tall, healthy, young males
  - secondary (underlying lung disease)
    - rupture of subpleural bleb which migrates along bronchialveolar sheath to the mediastinum then to the intrapleural space
    - necrosis of lung tissue adjacent to pleural surface (e.g. pneumonia, abscess, PCP, lung CA, emphysema)

Signs and Symptoms
- can be asymptomatic
- acute-onset pleuritic chest pain, dyspnea
tachypnea, tachycardia
- tracheal deviation (contralateral deviation in tension pneumothorax)
- ipsilateral diminished chest expansion
- decreased tactile/vocal fremitus
- hyperresonance
- ipsilateral diminished breath sounds

**Investigations**
- CXR
  - small: separation of visceral and parietal pleura seen as fine crescentic line parallel to chest wall at apex
  - large: increased density and decreased volume of lung on side of pneumothorax
  - see Medical Imaging, MI8

**Treatment**
- small pneumothoraces (<20% with no signs of respiratory/circulatory collapse) resolve spontaneously; breathing 100% oxygen accelerates resorption of air
- small intercostal tube with Heimlich valve for most spontaneous pneumothoraces
- large pneumothoraces or those complicating underlying lung disease require placement of a chest tube connected to underwater seal ± suction
- for repeated episodes: pleurodesis with sclerosing agent or apical bullectomy and abrasion
- treat underlying cause (e.g. antibiotic for PCP)

### Asbestos-Related Pleural Disease and Mesothelioma

**Etiology and Pathophysiology**
- benign manifestations of asbestos exposure
  - “benign asbestos pleural effusion”
  - exudative effusion, typically ~10 yr after exposure, resolves
  - pleural plaques, usually calcified
  - marker of exposure; usually an asymptomatic radiologic finding
- mesothelioma
  - primary malignancy of the pleura
  - decades after asbestos exposure (even with limited exposure)
  - smoking not a risk factor, but asbestos and smoking synergistically increase risk of lung cancer

**Signs and Symptoms**
- persistent chest pain, dyspnea, cough, bloody pleural effusion, weight loss

**Investigations**
- biopsy (pleuroscopic or open)
- needle biopsy may seed needle tract with tumour

**Treatment**
- resection (extrapleural pneumonectomy) requires careful patient selection; rarely successful (average survival <1 yr)

### Respiratory Failure

**Definition**
- failure of respiratory system to maintain normal blood gases
- hypoxemic ($P_O_2 < 60$ mmHg)
- hypercapnic ($P_CO_2 > 50$ mmHg)
- acute vs. chronic (compensatory mechanisms activated)

**Signs and Symptoms**
- signs of underlying disease
- hypoxemia: restlessness, confusion, cyanosis, coma, cor pulmonale
- hypercapnia: headache, dyspnea, drowsiness, asterixis, warm periphery, plethora, increased ICP (secondary to vasodilatation)

**Investigations**
- serial ABGs
- CXR and/or CT, bronchoscopy to characterize underlying cause if unclear
Hypoxemic Respiratory Failure

Definition
- PaO₂ decreased, PaCO₂ normal or decreased

Treatment
- reverse the underlying pathology
- oxygen therapy: maintain oxygenation (if shunt present, supplemental O₂ is less effective; see Anesthesia, A9, for oxygen delivery systems)
- ventilation, BiPAP, and PEEP/CPAP (see Anesthesia, A10): positive pressure can recruit alveoli and redistribute lung fluid
- improve cardiac output: ± hemodynamic support (fluids, vasopressors, inotropes), reduction of O₂ requirements

<table>
<thead>
<tr>
<th>Table 27. Approach to Hypoxemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Hypoxemia</strong></td>
</tr>
<tr>
<td>1. Low FIO₂</td>
</tr>
<tr>
<td>2. Hypoventilation</td>
</tr>
<tr>
<td>3a. Shunt</td>
</tr>
<tr>
<td>3b. Shunt (Right to Left)</td>
</tr>
<tr>
<td>4. Low Mixed Venous O₂ Content</td>
</tr>
<tr>
<td>5. V/Q Mismatch</td>
</tr>
<tr>
<td>6. Diffusion Impairment</td>
</tr>
</tbody>
</table>

In chronic hypercapnia, supplemental O₂ may decrease the hypoxic drive to breathe, but do not deny oxygen if the patient is hypoxic

Hypercapnic Respiratory Failure

- PaCO₂ increased, PaO₂ decreased

Pathophysiology
- increased CO₂ production: fever, sepsis, seizure, acidosis, carbohydrate load
- alveolar hypoventilation: COPD, asthma, CF, chest wall disorder, dead space ventilation (rapid shallow breathing)  
  - inefficient gas exchange results in inadequate CO₂ removal in spite of normal or increased minute volume
- hypoventilation
  - central: brainstem stroke, hypothyroidism, severe metabolic alkalosis, drugs (opiates, benzodiazepines)
  - neuromuscular: myasthenia gravis, Guillain-Barré, phrenic nerve injury, muscular dystrophy, polymyositis, kyphoscoliosis
  - muscle fatigue

Treatment
- reverse the underlying pathology
- if PaCO₂ >50 mmHg and pH is acidemic consider noninvasive or mechanical ventilation
- correct exacerbating factors
  - NTT/ETT suction: clearance of secretions
  - bronchodilators: reduction of airway resistance
  - antibiotics: treatment of infections
- maintain oxygenation (see above)
- diet: increased carbohydrate can increase PaCO₂ in those with mechanical or limited alveolar ventilation; high lipids decrease PaCO₂

Dead Space
- Ventilation without perfusion
- The opposite of shunt

Causes of Hypercapnia
- High Inspired CO₂
- Low Total Ventilation
- High Deadspace Ventilation
- High CO₂ Production

In COPD patients with chronic hypercapnia (“CO₂ retainers”), provide supplemental oxygen to achieve target SaO₂ from 88-92%
Acute Respiratory Distress Syndrome

- clinical syndrome characterized by severe respiratory distress, hypoxemia, and noncardiogenic pulmonary edema
- The Berlin Criteria (JAMA 2012; 307:2526-2533) for ARDS
  - acute onset
    - within 7 d of a defined event, such as sepsis, pneumonia, or patient noticing worsening of respiratory symptoms
      - usually occurs within 72 h of presumed trigger
  - bilateral opacities consistent with pulmonary edema on either CT or CXR
  - not fully explained by cardiac failure/fluid overload, but patient may have concurrent heart failure
  - objective assessment of cardiac function (e.g. echocardiogram) should be performed even if no clear risk factors

Etiology
- direct lung injury
  - airway: aspiration (gastric contents, drowning), pneumonia, inhalation injury (oxygen toxicity, nitrogen dioxide, smoke)
  - circulation: embolism (fat, amniotic fluid), reperfusion injury
- indirect lung injury
  - circulation: sepsis, shock, trauma, blood transfusion, pancreatitis
  - neurogenic: head trauma, intracranial hemorrhage, drug overdose (narcotics, sedatives, TCAs)

Pathophysiology
- disruption of alveolar capillary membranes \(\rightarrow\) leaky capillaries \(\rightarrow\) interstitial and alveolar pulmonary edema \(\rightarrow\) reduced compliance, V/Q mismatch, shunt, hypoxemia, pulmonary HTN

Clinical Course
A. Exudative Phase
- first 7 d of illness after exposure to ARDS precipitant
- alveolar capillary endothelial cells and type I pneumocytes are injured, resulting in loss of normally tight alveolar barrier
- patients develop dyspnea, tachypnea, increased work of breathing
  - these result in respiratory fatigue and eventually respiratory failure (see Hypoxemic Respiratory Failure, R26)

B. Fibroproliferative Phase
- after day 7
  - may still experience dyspnea, tachypnea, fatigue, and hypoxemia
  - most patients clinically improve and are able to wean off mechanical ventilation
  - some patients develop fibrotic lung changes that may require long-term support on supplemental oxygen or even mechanical ventilation
  - if fibrosis present, associated with increased mortality

Treatment
- based on ARDS network (see Landmark Respirology Trials, R36)
- treat underlying disorder (e.g. antibiotics if infection present)
- mechanical ventilation using low tidal volumes (<6 mL/kg) to prevent barotrauma
  - use optimal amount of PEEP (positive end-expiratory pressure) to keep airways open and allow the use of lower F\textsubscript{O\textsubscript{2}}
  - may consider using prone ventilation, and/or inhaled nitric oxide, high frequency oscillator or ECMO (extracorporeal membrane oxygenation) if conventional treatment is failing
- fluids and inotropic therapy (e.g. dopamine, vasopressin) if cardiac output inadequate
- pulmonary-arterial catheter now seldom used for monitoring hemodynamics
- mortality: 30–40%, usually due to non-pulmonary complications
- sequelae of ARDS include residual pulmonary impairment, severe debilitation, polyneuropathy and psychologic difficulties, which gradually improve over time
- most survivors eventually regain near-normal lung function, often with mildly reduced diffusion capacity

Risk Factors for Aspiration Pneumonia

<table>
<thead>
<tr>
<th>Categories</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased level of consciousness</td>
<td>Alcoholism</td>
</tr>
<tr>
<td>Upper GI tract disorders</td>
<td>Dysphagia, esophageal disorders</td>
</tr>
<tr>
<td>Mechanical instrumentation</td>
<td>Intubation, nasogastric tube, feeding tubes</td>
</tr>
<tr>
<td>Neurologic conditions</td>
<td>Dementia, Parkinson disease</td>
</tr>
<tr>
<td>Others</td>
<td>Protracted vomiting</td>
</tr>
</tbody>
</table>

ALI vs. ARDS: Definition is the same, except ALI is a \(\text{PaO}_2/\text{FiO}_2 \leq 300\), while ARDS is a \(\text{PaO}_2/\text{FiO}_2 \leq 200\)

Categorization of ARDS as Mild, Moderate or Severe – The Berlin Criteria

<table>
<thead>
<tr>
<th>ARDS Severity</th>
<th>(\text{PaO}_2/\text{FiO}_2) (mmHg)</th>
<th>Mortality (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>200-300</td>
<td>27 (24-30)%</td>
</tr>
<tr>
<td>Moderate</td>
<td>100-200</td>
<td>32 (29-34)%</td>
</tr>
<tr>
<td>Severe</td>
<td>&lt;100</td>
<td>45 (42-48)%</td>
</tr>
</tbody>
</table>

*on \(\geq 5\) cm H\textsubscript{2}O PEEP, \#P<0.001
JAMA 2012;307:2526-2533
Neoplasms

Lung Cancer

Classification
- Lung tumours can be classified as primary or secondary, benign or malignant, endobronchial or parenchymal.
- Bronchogenic carcinoma (epithelial lung tumours) is the most common type of primary lung tumour (other types make up less than 1%).
  - Small cell lung cancer (SCLC): 10-15%
  - Non-small-cell lung cancer (NSCLC): 85-90%
- Squamous cell carcinoma: arise from the proximal respiratory epithelium.
- Adenocarcinoma: incidence is increasing; most common subtype in nonsmokers
- Bronchoalveolar carcinoma: grows along the alveolar wall in the periphery; may arise at sites of previous lung scarring.
- Large cell undifferentiated cancer: diagnosis of exclusion.
- Benign epithelial lung tumours can be classified as papillomas or adenomas.

Table 28. Characteristics of Bronchogenic Cancer

<table>
<thead>
<tr>
<th>Cell Type</th>
<th>Incidence</th>
<th>Correlation with Smoking</th>
<th>Location</th>
<th>Histology</th>
<th>Metastasis</th>
<th>5 Yr Survival Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCLC</td>
<td>10-15%</td>
<td>Strong</td>
<td>Central</td>
<td>oat cell, neuroendocrine</td>
<td>Disseminated at presentation</td>
<td>Origin in endobronchial cells</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>M: 35%</td>
<td>Weak</td>
<td>Peripheral</td>
<td>Glandular, mucin producing</td>
<td>Early, distant</td>
<td>12% (60% for bronchoalveolar carcinoma, a subtype, with a resectable solitary lesion)</td>
</tr>
<tr>
<td>Squamous Cell Carcinoma (SCC)</td>
<td>30%</td>
<td>Strong</td>
<td>Central</td>
<td>Keratin, intercellular bridges</td>
<td>Local invasion and distant spread, may cavitate</td>
<td>25%</td>
</tr>
<tr>
<td>Large Cell Carcinoma</td>
<td>10-15%</td>
<td>Strong</td>
<td>Peripheral</td>
<td>Anaplastic, undifferentiated</td>
<td>Early, distant</td>
<td>13%</td>
</tr>
</tbody>
</table>

Risk Factors
- Cigarette smoking: the relative risk of developing lung cancer is 10-30 times higher for smokers than for nonsmokers.
- Other risk factors include: tobacco smoking, pipe smoking, second-hand smoke, asbestos, and exposure to asbestos.
- Risks associated with smoking include: chronic cough, hoarseness, lung cancer, and chronic obstructive pulmonary disease.
- Risks associated with asbestos exposure include: lung cancer, mesothelioma, and asbestosis.

Signs and Symptoms
- May be due to primary lesion, metastasis, or paraneoplastic syndrome.
- Primary lesion: cough, dyspnea, chest pain, hemoptysis.
- Metastasis: bone pain, weight loss, fever, anemia.
- Paraneoplastic syndromes: anorexia, weight loss, fever, anemia.

Summary of Recommendations on Screening for Lung Cancer

| American College of Chest Physicians (2013) | Screening with CXR | Not recommended |
| American Lung Association (2013)           | Screening with CXR | Not recommended |

Reduced Lung Cancer Mortality with Low-Dose CT Screening

| Study: Multicentre, RCT. | Methods: 2,058 participants at high risk for lung cancer (55-74 yr, >30 yr smoking), and smoking cessation for <5 y | Low-dose CT |
| Study: Multicentre, RCT. | Rate of positive screening test 24.2% 6.9% |
| Study: Multicentre, RCT. | False positives 96.4% 94.5% |
| Study: Multicentre, RCT. | Incidence of lung cancer Death from lung cancer |
| Study: Multicentre, RCT. | Person yr | Person yr |
| Study: Multicentre, RCT. | Person yr | Person yr |
| Conclusions: Screening with low-dose CT reduces mortality from lung cancer. |

Horner has a MAP of the Coast
A Pancoast tumour compresses the cervical sympathetic plexus causing a Horner’s syndrome:
- Miosis
- Anhydrosis
- Ptosis
### Table 29. Paraneoplastic Syndromes

<table>
<thead>
<tr>
<th>System</th>
<th>Clinical Presentation</th>
<th>Associated Malignancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal</td>
<td>Clubbing, hypertrophic pulmonary osteoarthropathy (HPOA)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Acanthosis nigricans</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hypercalcemia (osteolytic or PTHrP)</td>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td></td>
<td>Hypophosphatemia</td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Cushing’s syndrome (ACTH)</td>
<td>SCLC</td>
</tr>
<tr>
<td>Neuromyopathic</td>
<td>Lambert-Eaton syndrome</td>
<td>SCLC</td>
</tr>
<tr>
<td>Vascular/</td>
<td>Nonbacterial endocarditis</td>
<td>Bronchogenic cancer</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Trousseau’s syndrome (migratory thrombophlebitis)</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Renal</td>
<td>Nephrotic syndrome</td>
<td></td>
</tr>
</tbody>
</table>

### Investigations

- **Initial diagnosis**
  - Imaging: CXR, CT chest + upper abdomen, PET scan, bone scan
  - Cytology: sputum
  - Biopsy: bronchoscopy, EBUS, CT-guided percutaneous needle biopsy, mediastinoscopy
- **Staging workup**
  - TMN staging system: T – primary tumour (size); N – regional lymph nodes; M – distant metastasis
  - Blood work: electrolytes, LFTs, calcium, ALP
  - Imaging: CXR, CT thorax and upper abdomen, bone scan, neuroimaging
  - Invasive: bronchoscopy (EBUS), mediastinoscopy, mediastinotomy, thoracotomy
  - Screen adenocarcinoma for EGFR and ALK mutations

### Table 30. SCLC vs. NSCLC

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
<th>Treatment</th>
<th>Median Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCLC</strong></td>
<td>Limited stage</td>
<td>Radiation ± chemotherapy ± prophylactic to brain</td>
<td>1-2 yr</td>
</tr>
<tr>
<td></td>
<td>Extensive stage</td>
<td>Chemotherapy</td>
<td>6 mo</td>
</tr>
<tr>
<td><strong>NSCLC</strong></td>
<td>IA</td>
<td>T1a-1bN0M0</td>
<td>50-73</td>
</tr>
<tr>
<td></td>
<td>IB</td>
<td>T2aN0M0</td>
<td>43-58</td>
</tr>
<tr>
<td></td>
<td>IIA</td>
<td>T1a-T2a,N1M0 or T2bN0M0</td>
<td>36-46</td>
</tr>
<tr>
<td></td>
<td>IIB</td>
<td>T2bN1M0 or T3N0M0</td>
<td>25-36</td>
</tr>
<tr>
<td></td>
<td>IIIA</td>
<td>T1a-T2bN2M0 or T3N1-2M0 or T4N0-1M0</td>
<td>19-24</td>
</tr>
<tr>
<td></td>
<td>IIIIB</td>
<td>T4N2M0 or T1-4N3M0</td>
<td>7-9</td>
</tr>
<tr>
<td></td>
<td>IV</td>
<td>T1-4N0-3M1a-1b</td>
<td>2-13</td>
</tr>
</tbody>
</table>

* Depending on clinical vs. pathologic stage.*

### Treatment

- Options include surgery, radiotherapy, chemotherapy, and palliative care for end-stage disease.
- Surgery not usually performed for SCLC since it is generally non-curable.
- Contraindications for surgery:
  - Spread to contralateral lymph nodes or distant sites
  - Patients with potentially resectable disease must undergo mediastinal node sampling since CT thorax is not accurate in 20-40% of cases.
  - Poor pulmonary status (e.g., unable to tolerate resection of lung).

### Prevention

- Smoking cessation
- Avoidance of exposures
- Early detection

Malignant lung tumours are the most common cause of cancer mortality throughout the world in both men and women.
• chemotherapy (used in combination with other treatments)
  ▪ common agents: etoposide, platinum agents (e.g. cisplatinum), ifosfamide, vincristine, anthracyclines, paclitaxel, irinotecan, gefitinib (an endothelial growth factor receptor inhibitor)
  ▪ complications
    • acute: tumour lysis syndrome, infection, bleeding, myelosuppression, hemorrhagic cystitis (cyclophosphamide), cardiotoxicity (doxorubicin), renal toxicity (cisplatin), peripheral neuropathy (vincristine)
    • chronic: neurologic damage, leukemia, additional primary neoplasms

**Approach to the Solitary Pulmonary Nodule**

• see Medical Imaging, MI7

**Definition**

• a round or oval, sharply circumscribed radiographic lesion up to 3-4 cm, which may or may not be calcified, and is surrounded by normal lung

• can be benign or malignant

**Table 31. Differential Diagnosis for Benign vs. Malignant Solitary Nodule**

<table>
<thead>
<tr>
<th>Benign (70%)</th>
<th>Malignant (30%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious granuloma (histoplasmosis, coccidiomycosis, TB, atypical mycobacteria)</td>
<td>Bronchogenic carcinoma</td>
</tr>
<tr>
<td>Other infections (bacterial abscess, PCP, aspergillosis)</td>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Benign neoplasms (hamartoma, lipoma, fibroma)</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>Vascular (AV malformation, pulmonary varix)</td>
<td>Large cell carcinoma</td>
</tr>
<tr>
<td>Developmental (bronchogenic cyst)</td>
<td>Small cell carcinoma</td>
</tr>
<tr>
<td>Inflammatory (granulomatosis with polyangiitis, rheumatoid nodule, sarcoidosis)</td>
<td>Metastatic lesions</td>
</tr>
<tr>
<td>Other (infarct, pseudotumour, rounded atelectasis, lymph nodes, amyloidoma)</td>
<td>Breast</td>
</tr>
<tr>
<td></td>
<td>Head and neck</td>
</tr>
<tr>
<td></td>
<td>Melanoma</td>
</tr>
<tr>
<td></td>
<td>Colon</td>
</tr>
<tr>
<td></td>
<td>Kidney</td>
</tr>
<tr>
<td></td>
<td>Sarcoma</td>
</tr>
<tr>
<td></td>
<td>Germ cell tumours</td>
</tr>
<tr>
<td></td>
<td>Pulmonary carcinoid</td>
</tr>
</tbody>
</table>

**Investigations**

• CXR: always compare with previous CXR
• CT densitometry and contrast enhanced CT of thorax
• sputum cytology: usually poor yield
• biopsy (bronchoscopic or percutaneous) or excision (thoracoscopy or thoracotomy): if clinical and radiographic features do not help distinguish between benign or malignant lesion
  ▪ if at risk for lung cancer, biopsy may be performed regardless of radiographic features
  ▪ if a biopsy is non-diagnostic, whether to observe, re-biopsy, or resect will depend on the level of suspicion
• watchful waiting: repeat CXR and/or CT scan at 3, 6, 12 mo
• PET scan can help distinguish benign from malignant nodules

**Table 32. CXR Characteristics of Benign vs. Malignant Solitary Nodule**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>&lt;3 cm, round, regular</td>
<td>&gt;3 cm, irregular, spiculated</td>
</tr>
<tr>
<td>Margins</td>
<td>Smooth margin</td>
<td>Ill-defined or notched margin</td>
</tr>
<tr>
<td>Features</td>
<td>Calcified pattern: central, “popcorn” pattern if hamartoma, usually no cavitation; if cavitating, wall is smooth and thin, no other lung pathology</td>
<td>Usually not calcified; if calcified, pattern is eccentric, no satellite lesions, cavitation with thick wall, may have pleural effusions, lymphadenopathy</td>
</tr>
<tr>
<td>Doubling Time</td>
<td>Doubles in &lt;1 mo or &gt;2 yr</td>
<td>Doubles in &gt;1 mo or &lt;2 yr</td>
</tr>
</tbody>
</table>

**Terminology**

• "nodule" <3 cm
• "mass" >3 cm

**Hamartomas**

• 10% of benign lung lesions
• Composed of tissues normally present in lung (fat, epithelium, fibrous tissue, and cartilage), but they exhibit disorganized growth
• Peak incidence is age 60, more common in men
• Usually peripheral and clinically silent
• CXR shows clustered "popcorn" pattern of calcification (pathognomonic for hamartoma)

Pulmonary neoplasms may present as a solitary pulmonary nodule identified incidentally on a radiographic study (~10% of cases) or as symptomatic disease (most cases)

Adenocarcinoma present in a non-smoker may be due to endothelial growth factor receptor mutation

Corona Radiata Sign on Chest CT

• Fine striations that extend linearly from a nodule in a spiculated fashion
• Highly associated with malignancy
Sleep-Related Breathing Disorders

Hypoventilation Syndromes

- primary alveolar hypoventilation: idiopathic
- obesity-hypoventilation syndrome (Pickwickian syndrome)
- respiratory neuromuscular disorders

Sleep Apnea

Definition
- episodic decreases in airflow during sleep
- quantitatively measured by the Apnea/Hypopnea Index (AHI) = # of apneic and hypopneic events per hour of sleep
- sleep apnea generally accepted to be present if AHI >15

Classification
- obstructive (OSA)
  - caused by transient, episodic obstruction of the upper airway
  - absent or reduced airflow despite persistent respiratory effort
- central (CSA) (see Neurology, N49)
  - caused by transient, episodic decreases in CNS drive to breathe
  - no airflow because no respiratory effort
  - Cheyne-Stokes Respiration: a form of CSA in which central apneas alternate with hyperpneas to produce a crescendo-decrescendo pattern of tidal volume; seen in severe LV dysfunction, brain injury, and other settings (see Figure 2)
- mixed (MSA)
  - features of both OSA and CSA
  - loss of hypoxic and hypercapnic drives to breathe secondary to “resuscitative breathing”: overcompensatory hyperventilation upon awakening from OSA induced hypoxia

Risk Factors
- for OSA: obesity, upper airway abnormality, neuromuscular disease, hypothyroidism, alcohol/sedative use, nasal congestion, sleep deprivation
- for CSA: LV failure, brainstem lesions, encephalitis, encephalopathy, myxedema, high altitude

Signs and Symptoms
- obtain history from spouse/partner
- secondary to repeated arousals and fragmentation of sleep: daytime somnolence, personality and cognitive changes, snoring
- secondary to hypoxemia and hypercapnia: morning headache, polycythemia, pulmonary/systemic HTN, cor pulmonale/CHF, nocturnal angina, arrhythmias

Figure 12. Evaluation of a solitary pulmonary nodule

Solitary pulmonary nodule

Check previous CXR

Significant risk factor on Hx
Looks malignant or changed
CT thorax
Infection
Bronchoscopy
Stage and treat
Cancer
Calcification
Observe
PET scan
Transthoracic needle biopsy
Follow with serial CT
Cancer
Inflammatory
Still no diagnosis ± growing
Stage and treat
Treat cause
Biopsy or resect for diagnosis

Carcinoids
- Early onset (40-60 yr)
- Most are central and can produce symptoms and signs of bronchial obstruction
- Hemoptysis is present in ~50% of cases

Normal Respiratory Changes during Sleep
- Tidal volume decreases
- Arterial CO₂ increases (due to decreased minute ventilation)
- Pharyngeal dilator muscles relax causing increased upper airway resistance

Apnea: absence of breathing for ≥10 s
Hypopnea: excessive decrease in rate or depth of breathing (>50% reduction in ventilation)
Hypercnea: excessive increase in rate or depth of breathing
• the typical presentation for OSA is a middle-aged obese male who snores
• CSA can be due to neurological disease

Investigations
• sleep study (polysomnography)
  • evaluates sleep stages, airflow, ribcage movement, ECG, SaO₂, limb movements
• indications
  • excessive daytime sleepiness
  • unexplained pulmonary HTN or polycythemia
  • daytime hypcapnia
  • titration of optimal nasal CPAP
  • assessment of objective response to other interventions

Treatment
• modifiable factors: weight loss, decreased alcohol/sedatives, nasal decongestion, treatment of underlying medical conditions
• OSA or MSA: nasal CPAP, postural therapy (e.g. no supine sleeping), dental appliance, uvulopalatopharyngoplasty, tonsillectomy
• CSA or hypventilation syndromes: nasal BiPAP/CPAP, respiratory stimulants (e.g. progesterone) in select cases
• tracheostomy rarely required and should be used as last resort for OSA

Complications
• depression, weight gain, decreased quality of life, workplace and vehicular accidents, cardiac complications (e.g. HTN), reduced work/social function

Introduction to Intensive Care

• goal is to provide stabilization for critically ill patients: hemodynamic, respiratory or cardiac instability, or need for close monitoring

Intensive Care Unit Basics

Lines and Catheters
• arterial lines
  • monitor beat-to-beat blood pressure variations, obtain blood for routine ABGs
  • common sites are the radial and femoral arteries
• central venous catheter (central line)
  • administer IV fluids, monitor CVP, insert pulmonary artery catheters
  • administer TPN and agents too irritating for peripheral line
  • common sites: internal jugular vein, subclavian vein, femoral vein
• pulmonary arterial catheter
  • balloon guides the catheter from a major vein to the right heart
  • measures pulmonary capillary wedge pressure (PCWP) via a catheter wedged in distal pulmonary artery
  • PCWP reflects the LA and LV diastolic pressure (barring pulmonary venous or mitral valve disease)
• indications (now used infrequently due to associated complications)
  • diagnosis of shock states, primary pulmonary HTN, valvular disease, intracardiac shunts, cardiac tamponade, PE
  • assessment of hemodynamic response to therapies
  • differentiation of high- versus low-pressure pulmonary edema
  • management of complicated MI, multiorgan system failure and/or severe burns, or hemodynamic instability after cardiac surgery
• absolute contraindications
  • tricuspid or pulmonary valve mechanical prosthesis
  • right heart mass (thrombus or tumour)
  • tricuspid or pulmonary valve endocarditis

Table 33. Useful Equations and Cardiopulmonary Parameters

<table>
<thead>
<tr>
<th>Equation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSA = [Ht (cm) + Wt (kg) – 60]/100</td>
<td>Body surface area</td>
</tr>
<tr>
<td>PCWP = LVEDP</td>
<td>Pulmonary capillary wedge pressure</td>
</tr>
<tr>
<td>SV = CO / HR</td>
<td>Stroke volume</td>
</tr>
<tr>
<td>SVI = CO / HR</td>
<td>Stroke volume index</td>
</tr>
<tr>
<td>CI = CO / BSA</td>
<td>Cardiac index</td>
</tr>
<tr>
<td>RV Ejection Fraction = SV / RVEDV</td>
<td>Right ventricular ejection fraction</td>
</tr>
<tr>
<td>SVRI = [(MAP – RAP) 80]/CI</td>
<td>Systemic vascular resistance index</td>
</tr>
<tr>
<td>P.F ratio = pO₂ / pCO₂</td>
<td>Arteriovenous oxygen content difference</td>
</tr>
<tr>
<td>MAP = 1/3 sBP + 2/3 dBP = dBP + 1/3 PP</td>
<td>Mean arterial pressure</td>
</tr>
</tbody>
</table>

BSA = body surface area; CI = cardiac index; CO = cardiac output; dBP = diastolic blood pressure; HR = heart rate; LVEDP = left ventricular end diastolic pressure; MAP = mean arterial pressure; PCWP = pulmonary capillary wedge pressure; PP = pulse pressure; RAP = right atrial pressure; RVEDV = right ventricular end diastolic volume; sBP = systolic blood pressure; SV = stroke volume; SVRI = systemic vascular resistance index; Wt = weight, Ht = height
### Organ Failure

**Table 34. Types of Organ Failure**

<table>
<thead>
<tr>
<th>Type of Failure</th>
<th>Clinical Presentation</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory Failure</td>
<td>Hypoxemia, Hypercapnea</td>
<td>Treat underlying cause (e.g. lung disease, shunt, V/Q mismatch, drug-related, cardiac) Manage mechanical ventilation settings Supplemental oxygen</td>
</tr>
<tr>
<td>Cardiac Failure</td>
<td>Hypotension, Decreased urine output, Altered mental status, Arhythmia, Hypoxia</td>
<td>Treat underlying cause (e.g. bradycardia, tachycardia, blood loss, adrenal insufficiency) Volume resuscitation Vasopressors Inotropes Intra-aortic balloon pump</td>
</tr>
<tr>
<td>Coagulopathy</td>
<td>Increased INR or PT, Low platelet count, Bleeding, bruising</td>
<td>Treat underlying cause (e.g. thrombocytopenia, drug-related, immune-related, DIC) Transfusion of blood products, clotting factors</td>
</tr>
<tr>
<td>Liver Failure</td>
<td>Elevated transaminases, bilirubin, Coagulopathy, Jaundice, Mental alteration (encephalopathy), Hypoglycemia</td>
<td>Treat underlying cause (e.g. viral hepatitis, drug related, metabolic) Liver transplant Lactulose</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>Elevated creatinine, Reduced urine output, Signs of volume overload (e.g. CHF, effusions)</td>
<td>Treat underlying cause (e.g. shock, drug-related, obstruction) Correct volume and electrolyte status, eliminate toxins Diuretics Dialysis</td>
</tr>
</tbody>
</table>

### Shock

- **see** [Emergency Medicine](#), ER3
- inadequate tissue perfusion potentially resulting in end organ injury
  - categories of shock
    - hypovolemic: hemorrhage, dehydration, vomiting, diarrhea, interstitial fluid redistribution
    - cardiogenic: myopathic (myocardial ischemia ± infarction), mechanical, arrhythmic, pharmacologic
    - obstructive: massive PE (saddle embolus), pericardial tamponade, constrictive pericarditis, increased intrathoracic pressure (e.g. tension pneumothorax)
    - distributive: sepsis, anaphylactic reaction, neurogenic, endocrinologic, toxic

**Table 35. Changes Seen in Different Classes of Shock**

<table>
<thead>
<tr>
<th></th>
<th>Hypovolemic</th>
<th>Cardiogenic</th>
<th>Obstructive</th>
<th>Distributive</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>↑</td>
<td>↑, N, or ↓</td>
<td>↑</td>
<td>↑ or ↓</td>
</tr>
<tr>
<td>BP</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>JVP</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td>Extremities</td>
<td>Cold</td>
<td>Cold</td>
<td>N or Cold</td>
<td>Warm</td>
</tr>
<tr>
<td>Other</td>
<td>Look for visible hemorrhage or signs of dehydration</td>
<td>Bilateral cracks on chest exam</td>
<td>Depending on cause, may see pulsus paradoxus, Kussmaul’s sign, or tracheal deviation</td>
<td>Look for obvious signs of infection or anaphylaxis</td>
</tr>
</tbody>
</table>

- treat underlying cause
- treatment goal is to return critical organ perfusion to normal (e.g. normalize BP)
- common treatment modalities include
  - fluid resuscitation
  - inotropes (e.g. dobutamine), vasopressors (e.g. norepinephrine), vasopressin
  - revascularization or thrombolytics for ischemic events

### Sepsis

- the leading cause of death in noncoronary ICU settings is multi-organ failure due to sepsis
- the predominant theory is that sepsis is attributable to uncontrollable immune system activation

**Definitions**

- sepsis: the presence of both infection and SIRS (see Table 36)
- severe sepsis: sepsis associated with organ dysfunction, hypoperfusion or hypotension
- septic shock: sepsis with arterial hypotension despite adequate fluid resuscitation
• multiorgan dysfunction syndrome: sepsis in the presence of altered organ function such that homeostasis cannot be maintained without intervention

Signs and Symptoms

Table 36. Clinical Manifestations of Sepsis

<table>
<thead>
<tr>
<th>General Variables</th>
<th>Organ Dysfunction Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (≥38°C) or hypothermia (&lt;36°C)</td>
<td>Arterial hypoxemia (P_{a}O_{2}/FiO_{2} &lt;300)</td>
</tr>
<tr>
<td>Heart rate &gt;90/min</td>
<td>Acute oliguria (urine output &lt;0.5 mL/kg/h)</td>
</tr>
<tr>
<td>sBP &lt;90 mmHg, MAP &lt;70, or a sBP decrease &gt;40 mmHg</td>
<td>Creatinine increase &gt;40 μmol/L</td>
</tr>
<tr>
<td>Tachypnea</td>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 s)</td>
</tr>
<tr>
<td>Altered mental status</td>
<td>Thrombocytopenia (platelet count &lt;100,000/L)</td>
</tr>
<tr>
<td>Positive fluid balance (&gt;20 mL/kg over 24 h)</td>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;70 mmol/L)</td>
</tr>
<tr>
<td>Hyperglycemia (BG &gt;7.7 mmol/L) in the absence of diabetes</td>
<td>Leukocytosis (WBC &lt;4,000/L)</td>
</tr>
<tr>
<td>Leukopenia (WBC &lt;4,000/L)</td>
<td></td>
</tr>
<tr>
<td>Normal WBC count with &gt;10% immature forms</td>
<td></td>
</tr>
<tr>
<td>Plasma C-reactive protein &gt;2 SD above the normal value</td>
<td></td>
</tr>
<tr>
<td>Arterial hypoxemia (P_{a}O_{2}/FiO_{2} &lt;300)</td>
<td></td>
</tr>
<tr>
<td>Acute oliguria (urine output &lt;0.5 mL/kg/h)</td>
<td></td>
</tr>
<tr>
<td>Creatinine increase &gt;40 μmol/L</td>
<td></td>
</tr>
<tr>
<td>Coagulation abnormalities (INR &gt;1.5 or aPTT &gt;60 s)</td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia (platelet count &lt;100,000/L)</td>
<td></td>
</tr>
<tr>
<td>Hyperbilirubinemia (plasma total bilirubin &gt;70 mmol/L)</td>
<td></td>
</tr>
<tr>
<td>Leukocytosis (WBC &lt;4,000/L)</td>
<td></td>
</tr>
</tbody>
</table>

Tissue Perfusion Variables

- Hyperlactatemia (>1 mmol/L)
- Decreased capillary refill or mottling


Treatment

- identify the cause and source of infection: blood, sputum, urine Gram stain, and C&S
- initiate empiric antibiotic therapy
- monitor, restore, and maintain hemodynamic function

Early Goal Directed Therapy

- adjustments of cardiac preload, afterload, and contractility to balance oxygen delivery with demand
- should be started immediately and completed within 6 h of recognition of severe sepsis or septic shock
- patient should meet SIRS criteria and sBP <90 mmHg or lactate >4 mmol/L
  1. supplemental oxygen ± intubation and mechanical ventilation
  2. central venous and arterial catheterization
  3. maintain CVP 8-12 mmHg with IV crystalloids/colloids
  4. MAP maintained 65-90 mmHg with the use of vasoactive agents
  5. Svo₂ <70% then
     - transfusion of red cells until Hct >30%
  - if Svo₂ <70% after transfusion then use inotropic agents
- supportive oxygenation and ventilation using lung-protective regimen
- early nutritional support: enteral route is used to preserve function of intestinal mucosal barrier
- control hyperglycemia with insulin to decrease infectious complications
- physiologic dose corticosteroid replacement therapy in patients with relative adrenal insufficiency (nonresponders to corticotropin stimulation test)
- consider in mechanically ventilated septic shock patients with organ dysfunction requiring vasopressors, despite early goal-directed therapy and appropriate antibiotic therapy
- recombinant activated protein C may be considered in patients with severe sepsis or septic shock with an APACHE II score >25 despite early goal-directed therapy and appropriate antibiotic therapy
- DVT/PE prophylaxis
- advanced care planning, including the communication of likely outcomes and realistic goals of treatment with patients and families

Corticosteroids for Treating Severe Sepsis and Septic Shock

Cochrane DB Syst Rev. 2010;CD002243

Study: Meta-analysis of 25 RCTs and quasi-RCTs examining the efficacy of corticosteroids on death at one month in patients with severe sepsis and septic shock.

Results: Overall, there was no difference in 28-d all-cause mortality but there was significant heterogeneity in dosing strategy between the studies. Treatment with long course of low dose corticosteroids significantly reduced 28-d mortality, increased the proportion of shock reversal by day 7 and day 28, reduced the sepsis-related organ failure assessment score by day 7, and survivors' length of stay in the ICU, without inducing gastrointestinal bleeding, superinfection, or neuromuscular weakness. Corticosteroids increased the risk of hyperglycemia and hypernatremia.

Conclusions: Corticosteroids did not change mortality in severe sepsis and septic shock. A long course of low dose corticosteroids reduced 28-d mortality without major complications.
### Table 37. Common Medications for Respiratory Diseases

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>β₂-AGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Short-Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>salbutamol/albuterol</td>
<td>1-2 puffs q4-6h prn</td>
<td>Bronchodilator in acute reversible airway obstruction</td>
<td>CV (angina, flushing, palpitations, tachycardia, can precipitate atrial fibrillation), CNS (dizziness, H/A, insomnia, anxiety), GI (diarrhea, N/V, rash, hypokalemia, paroxysmal bronchospasm)</td>
</tr>
<tr>
<td><strong>Long-Acting</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>salmeterol (Seretide®), formoterol (Oxave®)</td>
<td>1-2 puffs bid</td>
<td>Maintenance treatment (prevention of bronchospasm) in COPD, asthma</td>
<td></td>
</tr>
<tr>
<td>indacaterol (Orbex®)</td>
<td>1 puff daily</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Combination Long-Acting β₂-Agonist and Inhaled Corticosteroid</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluticasone and salmeterol (Advair®) (purple MDI or diskus)</td>
<td>1 puff bid</td>
<td>COPD and asthma</td>
<td>Common: CNS, H/A, dizziness Resp: URTI, GI (N/V, diarrhea, pain/discomfort, oral candidiasis)</td>
</tr>
<tr>
<td>Budesonide and formoterol (Symbicort®) (red turbuhaler)</td>
<td>2 puffs bid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mometasone and formoterol (Zentale®) (blue MDI)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTICHOLINERGICS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ipratropium bromide (Atrovent®) (clear/green), tiotropium bromide (Spiriva®), glycopyrronium bromide</td>
<td>2-3 puffs qid, 1 puff qam, 1 puff daily</td>
<td>Bronchodilator used in COPD, bronchitis and emphysema</td>
<td>Palpitations, anxiety, dizziness, fatigue, H/A, N/V, dry mucous membranes, urinary retention, increased toxicity in combination with other anticholinergic drugs</td>
</tr>
<tr>
<td><strong>CORTICOSTEROIDS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Inhaled</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>fluticasone (Flovent®) (orange/peach), budesonide (Pulmicort®), ciclesonide (Alvesco®), beclomethasone (QVAR®, Vanceril®), Mometasone (Asmanex®)</td>
<td>2-4 puffs bid, 2 puffs bid OD, 1-4 puffs bid (40 µg), 1-2 puffs bid (80 µg), 1 puff daily or bid</td>
<td>Maintenance treatment of asthma</td>
<td>H/A, fever, N/V, MSK pain, URTI, throat irritation, growth velocity reduction in children/adolescents, HPA axis suppression, increased pneumonia risk in COPD</td>
</tr>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prednisone (Apo-prednisone®, Deltasone®)</td>
<td>Typically 40-60 mg per day PO 125 mg q8h IV (sodium succinate) loading dose 2 mg/kg then 0.5-1 mg/kg q6h for 5 d</td>
<td>Acute exacerbation of COPD; severe, persistent asthma, PCP Status asthmaticus</td>
<td>Endocrine (hirsutism, DM/glucose intolerance, Cushing’s syndrome, HPA axis suppression), GI (increased appetite, indigestion), ocular (cataracts, glaucoma), edema, AVN, osteoporosis, H/A, psychiatric (anxiety, insomnia), easy bruising</td>
</tr>
<tr>
<td>methylprednisolone (Depo-Medrol®, Solu-Medrol®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>theophylline (Uraphyl®)</td>
<td>400-600 mg OD</td>
<td>Treatment of symptoms of reversible airway obstruction due to COPD</td>
<td>Gl upset, diarrhea, N/V, anxiety, H/A, insomnia, muscle cramp, tremor, tachycardia, PVS, arrhythmias Toxicity: persistent, repetitive vomiting, seizures</td>
</tr>
<tr>
<td>montelukast (Singular®), zafirlukast (Accolate®)</td>
<td>10 mg PO qhs, now only available as once daily slow release 20 mg bid</td>
<td>Prophylaxis and chronic treatment of asthma</td>
<td>H/A, dizziness, fatigue, fever, rash, dyspepsia, cough, flu-like symptoms</td>
</tr>
<tr>
<td>omalizumab (Xolair®)</td>
<td>150-375 mg SC q2-4wk</td>
<td>Moderate-severe persistent asthma</td>
<td>H/A, sinusitis, pharyngitis, URTI, viral infection, thrombocytopenia, anaphylaxis</td>
</tr>
<tr>
<td><strong>PDE5 INHIBITORS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ronflumast (Daxas®)</td>
<td>500 µg PO OD</td>
<td>Severe emphysema, with frequent exacerbations</td>
<td>Weight loss, suicidal ideation</td>
</tr>
<tr>
<td><strong>MONOCLONAL ANTIBODIES</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ADJUNCT AGENTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>LEUKOTRIENE ANTAGONISTS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>ANTIBIOTICS – COMMUNITY ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>erythromycin</td>
<td>250-500 mg PO tid x 7-10 d</td>
<td>Alternate to doxycycline or fluoroquinolone</td>
<td>GI (abdominal pain, diarrhea, N/V, H/A, prolonged QT, ventricular arrhythmias, hepatic impairment GI (diarrhea, N/V, abdominal pain), renal failure, deafness H/A, rash, GI (diarrhea, N/V, abnormal taste, heartburn, abdominal pain), increased urea</td>
</tr>
<tr>
<td>azithromycin</td>
<td>500 mg PO x 1 dose, then 250 mg OD x 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>clarithromycin</td>
<td>1,000 mg od or 500 mg PO bid x 7-10 d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>doxycycline</td>
<td>100 mg PO bid x 7-10 d</td>
<td>Alternate to macrolide or fluoroquinolone</td>
<td>Photosensitivity, rash, urticaria, anaphylaxis, diarrhea, enterocolitis, tooth discoloration in children</td>
</tr>
<tr>
<td>fluoroquinolone</td>
<td>500 mg PO OD x 7-10 d</td>
<td>Alternate to macrolide or doxycycline</td>
<td>CNS (dizziness, fever, H/A, GI (N/V, diarrhea, constipation), prolonged QT</td>
</tr>
</tbody>
</table>
Table 37. Common Medications for Respiratory Diseases (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Typical Adult Dose</th>
<th>Indications</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ANTIBIOTICS – HOSPITAL ACQUIRED PNEUMONIA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd gen Cephalosporin</td>
<td>ceftiraxone (Rocephin®)</td>
<td>1-2 g IV OD x 7-10 d</td>
<td>Combine with fluoroquinolone or macrolide</td>
</tr>
<tr>
<td>Fluoroquinolone</td>
<td>levofloxacin</td>
<td>750 mg PO OD x 5 d</td>
<td>Combine with 3rd gen cephalosporin</td>
</tr>
<tr>
<td></td>
<td>moxifloxacin</td>
<td>400 mg PO OD x 7 d (5 d for AECOPD)</td>
<td></td>
</tr>
<tr>
<td>Piperacillin/ Tazobactam (Tazocin®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>4.5 g IV q6-8h x 7-10 d</td>
<td>Suspect Pseudomonas</td>
</tr>
<tr>
<td>Vancomycin (Vancocin®)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 g IV bid x 7-10 d</td>
<td>Suspect MRSA</td>
</tr>
<tr>
<td>Macrolide</td>
<td>azithromycin</td>
<td>500 mg IV OD x 2 d, then 500 mg PO OD x 5 d</td>
<td>Suspect Legionella</td>
</tr>
<tr>
<td></td>
<td>clarithromycin</td>
<td>1,000 mg od or 500 mg PO bid x 7-10 d</td>
<td></td>
</tr>
<tr>
<td><strong>ICU MEDICATIONS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pressors/Inotropes</td>
<td>norepinephrine (Levophed®)</td>
<td>0.5-30 µg/min IV</td>
<td>Acute hypotension</td>
</tr>
<tr>
<td></td>
<td>phenylephrine</td>
<td>0.5 µg/kg/min IV</td>
<td>Severe hypotension</td>
</tr>
<tr>
<td></td>
<td>dobutamine</td>
<td>2-20 µg/kg/min IV</td>
<td>Inotropic support</td>
</tr>
<tr>
<td>Sedatives/Analgesia</td>
<td>fentanyl (opioid class)</td>
<td>50-100 µg then unlimited</td>
<td>Sedation and/or analgesia</td>
</tr>
<tr>
<td></td>
<td>propofol (anesthetic)</td>
<td>1-3 mg/kg then 0.3-5 mg/kg/h IV</td>
<td>Sedation and/or analgesia</td>
</tr>
</tbody>
</table>

See Infectious Diseases, ID26 – for the management of pulmonary tuberculosis

Landmark Respirology Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARDS Network</td>
<td>NEJM 2000; 342:1301-8</td>
<td>Mortality decreased in ARDS patients ventilated with a low tidal volume strategy</td>
</tr>
<tr>
<td>Berlin Criteria</td>
<td>JAMA 2012; 307:2526-33</td>
<td>The new definition of ARDS, better predicts mortality</td>
</tr>
<tr>
<td>CPAP and Apnea</td>
<td>NEJM 2005; 353:2025-33</td>
<td>CPAP ameliorates symptoms of sleep apnea but does not affect mortality in CHF</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>NEJM 2012; 366:1287-97</td>
<td>Fixed dose of rivoxabarin was non-inferior to standard therapy (Vit K antagonist) initial and long-term treatment of PE</td>
</tr>
<tr>
<td>Emphysema Treatment Trial</td>
<td>NEJM 2003; 348:2059-73</td>
<td>Lung volume reduction surgery benefits patients with upper lobe disease and low exercise capacity</td>
</tr>
<tr>
<td>IELCAP</td>
<td>NEJM 2006; 355:1763-71</td>
<td>High survival rate in patients with early stage lung cancer detected by low dose CT screening</td>
</tr>
<tr>
<td>Lung Health</td>
<td>JAMA 1994; 272:1497-505</td>
<td>Aggressive smoking intervention significantly decreases the age-related decline in FEV1 in middle-aged smokers with mild airways obstruction</td>
</tr>
<tr>
<td>OSCILLATE</td>
<td>NEJM 2013; 368: 795-805</td>
<td>Early high-frequency oscillatory ventilation in patients with moderate to severe ARDS might increase in-hospital mortality</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>NEJM 1978; 298:801-9</td>
<td>Intersitial lung disease subsets have different prognoses and response to treatment (e.g. desquamative but not usual interstitial pneumonia respond well to corticosteroids)</td>
</tr>
<tr>
<td>POET-COPD</td>
<td>NEJM 2011; 364:1093-103</td>
<td>Tiotropium decreases the number of moderate-to-severe exacerbations in comparison to salmeterol</td>
</tr>
<tr>
<td>REDUCE</td>
<td>JAMA 2013; 309:2223-2231</td>
<td>5 d course of glucocorticoids is non-inferior to a 14 d course for treatment of acute COPD exacerbations</td>
</tr>
<tr>
<td>ROFLUMILAST</td>
<td>Lancet 2009; 374:695-703</td>
<td>Leukotriene inhibitors improve FEV1 when used as add-on therapy in COPD patients on tiotropium or salmeterol</td>
</tr>
<tr>
<td>TORCH</td>
<td>NEJM 2007; 356:775-89</td>
<td>Combination of inhaled steroids and long-acting β2-agonists improves COPD symptoms, reduces exacerbations, and shows a trend to lowers mortality</td>
</tr>
<tr>
<td>UPLIFT</td>
<td>NEJM 2008; 359:1543-54</td>
<td>Tiotropium improves symptoms of COPD with fewer exacerbations, but does not affect FEV1 decline</td>
</tr>
</tbody>
</table>
Acronyms

Ab antibody
ACPA anti-citrullinated protein antibodies
Ag antigen
ANA antinuclear antibody
ANCA antineutrophil cytoplasmic antibody
Anti-RNP antinuclear protein
Anti-Sm anti-Smith antibodies
APLA antiphospholipid antibody syndrome
AS ankylosing spondylitis
AVN avascular necrosis
BUN blood urea nitrogen
CBC complete blood count
CCB calcium channel blocker
CCP cyclic citrullinated peptide
CMC carpometacarpal joint
CNS central nervous system
CTD connective tissue disease
CPPD calcium pyrophosphate dihydrate
CRP C-reactive protein
DEXA dual energy X-ray absorptiometry
DP distal interphalangeal joint
DM diabetes mellitus
DMARD disease-modifying anti-rheumatic drug
DMX dermatomyositis
dsDNA double stranded DNA
EA enteropathic arthritis
ECASA enteric-coated acetylsalicylic acid
ESR erythrocyte sedimentation rate
GC Neisseria gonorrhoeae/gonococcus
GCA giant cell arthritis
GPA granulomatosis with polyangiitis
H/A headache
HB hemoglobin
HLA human leukocyte antigen
IA intra-articular
IBD inflammatory bowel disease
IE infectious endocarditis
ILD interstitial lung disease
ITP idiopathic thrombocytopenia purpura
MCP metacarpal phalangeal joint
MCTD mixed connective tissue disease
MHC major histocompatibility complex
MPO myeloperoxidase
MTP metatarsal phalangeal joint
MTX methotrexate
OA osteoarthritis
PAN polyarteritis nodosa
PP proximal interphalangeal joint
PM polynephritis
PMN polymorphonuclear leukocyte
PMR polymyalgia rheumatica
Psa psoriatic arthritis
PTT partial thromboplastin time
PUD peptic ulcer disease
RA rheumatoid arthritis
RBC red blood cell
ReA reactive arthritis
RF rheumatoid factor
ROM range of motion
Si sacriﬁcic
SLE systemic lupus erythematosus
SNRI serotonin–norepinephrine reuptake inhibitors
SS Sjögren’s syndrome
SSA Sjögren’s syndrome antigen A
SSB Sjögren’s syndrome antigen B
TNF tumour necrosis factor
U/A urinalysis
ULN upper limit of normal
U-SpA undifferentiated spondyloarthropathy
VDRL venereal disease research laboratory
WBC white blood cell
Anatomy of Joint Pathology

- Normal Joint
- Degenerative Joint
- Inflammatory Joint

Basics of Immunology

Immunogenetics and Disease

- cell surface molecules called HLAAs play a role in mediating immune reactions
- MHC are genes on the short arm of chromosome 6 that encode HLA molecules
- certain HLA haplotypes are associated with increased susceptibility to autoimmune diseases

Table 1. Mechanisms of Immunologically Mediated Disorders

<table>
<thead>
<tr>
<th>Type</th>
<th>Pathophysiology</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate Hypersensitivity</td>
<td>Formation of Ige → release of IgE bound to mast cells and T-cells → diffuse inflammation</td>
<td>Asthma, allergic rhinitis, anaphylaxis</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>Formation of Ab on cell surface → phagocytosis or lysis of target cell</td>
<td>Autoimmune hemolytic anemia, Goodpasture’s syndrome, Graves’ disease, pemphigus vulgaris, rheumatic fever, ITP</td>
</tr>
<tr>
<td>Immune Complex</td>
<td>Formation and deposition of Ag:Ab complexes → activate complement → leukocyte recruitment and activation → tissue injury</td>
<td>SLE, PAN, post-streptococcal glomerulonephritis, serum sickness, viral hepatitis</td>
</tr>
<tr>
<td>Cell-Mediated/Delayed</td>
<td>Release of cytokines by sensitized T-cells and T-cell mediated cytotoxicity</td>
<td>Contact dermatitis, insect venom, mycobacterial proteins</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Classes of MHCs

<table>
<thead>
<tr>
<th>MHC Class</th>
<th>Types</th>
<th>Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>HLA-A, B, C</td>
<td>All cells</td>
<td>Recognized by CD8+ (cytotoxic) T-lymphocytes</td>
</tr>
<tr>
<td>II</td>
<td>HLA-DP, DQ, DR</td>
<td>Ag presenting cells (mononuclear phagocytes, B cells, etc.)</td>
<td>Recognized by CD4+ (helper) T-lymphocytes</td>
</tr>
<tr>
<td>III</td>
<td>Some components of the complement cascade</td>
<td>In plasma</td>
<td>Chemotaxis, opsonization, lysis of bacteria and cells</td>
</tr>
</tbody>
</table>

Table 3. HLA-Associated Rheumatic Disease

<table>
<thead>
<tr>
<th>HLA Type</th>
<th>Associated Conditions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>B27</td>
<td>AS</td>
<td>In AS, relative risk = 70-90x</td>
</tr>
<tr>
<td></td>
<td>ReA</td>
<td>In ReA, relative risk = 40x</td>
</tr>
<tr>
<td>DR4, DR1</td>
<td>RA</td>
<td>In RA, relative risk = 2-10x; found in 93% of patients</td>
</tr>
<tr>
<td>DR3</td>
<td>SS</td>
<td>DR3 associated with many non-rheumatic conditions (celiac disease, type 1 DM, Graves’ disease, chronic active hepatitis)</td>
</tr>
</tbody>
</table>

Terminology in Rheumatology

Arthritis
- Joint swelling: effusion/synovial thickening
- Decreased ROM
- Stress pain (pain at the end of ROM)
- Increased warmth

Arthralgia: perception of joint pain without obvious clinical findings

Active Joint: swollen joint, joint line tenderness, or stress pain

Innate Immune Cells
- Neutrophil (PMN): circulate in blood and respond to inflammatory stimuli, kill invading organisms by phagocytosis, degranulation and neutrophil extracellular traps
- Natural Killer Cell: innate immunity against intracellular infections (especially viruses), killing function and produce cytokines
- Macrophage: arrive after PMNs, suppress PMN efflux and phagocytose PMN debris, secrete pro-inflammatory cytokines in response to microbial debris
- Dendritic Cell: actively phagocytic when immature, activated by signals from toll-like receptor (TLR), release pro-inflammatory cytokines, present antigens to T cells in lymph nodes
- Cosinophil: respond to inflammatory cytokines and degranulate releasing reactive oxygen species, and cytokines, associated with allergy, asthma and parasitic infection
- Mast Cell: present in connective tissue and mucosa, allergen cross-linking of IgE bound to mast cell triggers degranulation and release of inflammatory mediators

Adaptive Immune Cells
- B Cell: produce antibodies after activation by specific antigen and B-cell co-receptor, additional signals provided by CD4 T helper cells
- Cytotoxic T Cell: CD8, direct cytotoxicity of target cells at sites of infection, kill via lytic granules and FasL-Fas interaction, recognize specific antigen and MHC1
- Helper T Cell: subset of CD4 cells, activate and help other types of cells carry out immune defense (activate macrophages, help B cells, release cytokines)
- Regulatory T Cell: Subset of CD4 cells, suppress activation of naive autoreactive T cells

Key Cytokine Targets of Biologic Drugs

TNF
- Source: T cells, macrophages
- Major Functions: cachexia, induces other cytokines, T cell stimulation, induces metalloproteinases and prostaglandins, increases expression of adhesion molecules, increases vascular permeability leading to increased entry of IgG, complement and cells into tissues

IL-6
- Source: Many cells
- Major Functions: proliferation of B and T cells, acute phase reactant, induces natural protease inhibitor
### Differential Diagnoses of Common Presentations

**Figure 2. Clinical approach to joint pain**

#### Table 4. Differential Diagnosis of Monoarthritis

<table>
<thead>
<tr>
<th>Infection</th>
<th>Crystal</th>
<th>Degenerative</th>
<th>Trauma</th>
<th>Neoplastic</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Septic arthritis</td>
<td>Gout</td>
<td>OA</td>
<td>Hemarthrosis</td>
<td>Tumour</td>
<td>Systemic inflammatory disease</td>
</tr>
<tr>
<td>(S. aureus, GC, fungi, TB)</td>
<td>Pseudogout</td>
<td>OA</td>
<td></td>
<td></td>
<td>Polymyalgia presenting with non-articular</td>
</tr>
<tr>
<td></td>
<td>Hydroxyapatite</td>
<td></td>
<td></td>
<td></td>
<td>symptoms first</td>
</tr>
</tbody>
</table>

**Table 5. Differential Diagnosis of Oligoarthritis/Polyarthritis**

<table>
<thead>
<tr>
<th>First presentation or flare of inflammatory arthritis</th>
<th>Seropositive inflammatory arthritis</th>
<th>Seronegative inflammatory arthritis</th>
<th>Degenerative OA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute (&lt;6 wk)</td>
<td>RA</td>
<td>AS</td>
<td>OA</td>
</tr>
<tr>
<td>Post-viral (parvovirus B19)</td>
<td>SLE</td>
<td>EA</td>
<td>PsA</td>
</tr>
<tr>
<td>Acute rheumatic fever</td>
<td>Scleroderma</td>
<td>ReA</td>
<td>ReA</td>
</tr>
<tr>
<td>Infectious (GC, non-GC)</td>
<td>DM/PM</td>
<td>Crystal (polyarticular gout)</td>
<td></td>
</tr>
<tr>
<td>Gout</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sarcoïdosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lyme disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 6. Symptoms of Inflammatory Arthritis vs. Degenerative Arthritis**

<table>
<thead>
<tr>
<th>Inflammatory</th>
<th>Degenerative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain at rest, relieved by motion</td>
<td>Pain with motion, relieved by rest</td>
</tr>
<tr>
<td>Morning stiffness &gt;1 h</td>
<td>Morning stiffness &lt;½ h</td>
</tr>
<tr>
<td>Warmth, swelling, erythema</td>
<td>Joint instability, buckling, locking</td>
</tr>
<tr>
<td>Malalignment/deformity</td>
<td>Bony enlargement, malalignment/deformity</td>
</tr>
<tr>
<td>Extra-articular manifestations</td>
<td>Evening pain</td>
</tr>
<tr>
<td>Nighttime awakening</td>
<td></td>
</tr>
</tbody>
</table>

**Table 7. Seropositive vs. Seronegative Rheumatic Diseases**

<table>
<thead>
<tr>
<th>Seropositive</th>
<th>Seronegative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td>F &gt; M</td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>Symmetrical</td>
</tr>
<tr>
<td>Small (PIP, MCP) and medium joints (wrist, knee, ankle, elbow) common DIP less often involved</td>
<td>Usually larger joints, lower extremities (exception: PsA)</td>
</tr>
<tr>
<td>Pelvic/Axial Disease</td>
<td>No (except for C-spine)</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>No</td>
</tr>
<tr>
<td>Extra-Articular</td>
<td>Nodules</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>Oral ulcers</td>
</tr>
<tr>
<td>Sicca</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>Dermatologic features</td>
</tr>
</tbody>
</table>
Common Investigations in Rheumatology
- general: CBC, electrolytes, Cr
- acute phase reactants: ESR, CRP, ferritin, albumin, fibrinogen, platelets
- complement (C3, C4)
- U/A to detect disease complications (proteinuria, active sediment)
- serology; see Table 10
- synovial fluid analysis
- radiology (plain film x-ray, CT, MRI, U/S, bone densitometry, angiography, bone scan)

Synovial Fluid Analysis
- synovial fluid is an ultrafiltrate of plasma plus hyaluronic acid; it lubricates joint surfaces and nourishes articular cartilage

Indications
- diagnostic: mandatory if septic arthritis suspected; advised if crystal arthritis or hemarthrosis suspected; advised if unexplained effusion in accessible joint
- therapeutic: drainage of blood, purulent or tense effusions; corticosteroid injection

Contraindications
- absolute: open lesion or suspected infection of overlying skin or soft tissue
- relative: bleeding diathesis, thrombocytopenia, prosthetic joint

Synovial Fluid Analysis
- ensure synovial fluid is described in terms of colour, clarity, viscosity, and quantity
- culture and gram stain (bacteria, mycobacteria, fungi)
- if only have 1 mL of fluid, prioritize culture and gram stain
- cell count and differential
- crystal examination (microscopy with polarized light)
  - gout (monosodium urate) → needle-shaped, negatively birefringent (bright yellow)
  - pseudogout (CPPD) → rhomboid-shaped, positively birefringent (pale blue)

Table 8. Synovial Fluid Analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal</th>
<th>Non-Inflammatory</th>
<th>Inflammatory</th>
<th>Infectious</th>
<th>Hemorrhagic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colour</td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Pale yellow</td>
<td>Yellow to white</td>
<td>Red/brown</td>
</tr>
<tr>
<td>Clarity</td>
<td>Clear</td>
<td>Clear</td>
<td>Opaque</td>
<td>Opaque</td>
<td>Sanguinous</td>
</tr>
<tr>
<td>Viscosity (due to hyaluronic acid)</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low or paradoxically high if purulent</td>
<td>Variable</td>
</tr>
<tr>
<td>WBC/mm³</td>
<td>&lt;200</td>
<td>&lt;2,000</td>
<td>&gt;2,000</td>
<td>Higher cell counts (particularly &gt;50,000) suggestive</td>
<td>Variable</td>
</tr>
<tr>
<td>% PMN</td>
<td>&lt;25%</td>
<td>&lt;25%</td>
<td>&gt;25%</td>
<td>&gt;75%</td>
<td>Variable</td>
</tr>
<tr>
<td>Culture/</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Usually positive</td>
<td>-</td>
</tr>
<tr>
<td>Gram Stain</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Examples</td>
<td>Trauma</td>
<td>Seropositives</td>
<td>S. aureus</td>
<td>Trauma</td>
<td>Hemophilia</td>
</tr>
<tr>
<td></td>
<td>Osteoarthropathy</td>
<td>Seronegatives</td>
<td>Gram negative</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hypertrophic – arthropathy</td>
<td>Crystal</td>
<td>CC → difficult to culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>arthropathies</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Choosing Wisely Canada
Recommendations
1. Do not order ANA as a screening test in patients without specific signs or symptoms of SLE or another CTD
2. Do not order an HLA-B27 unless spondyloarthritis is suspected based on specific signs or symptoms
3. Do not repeat DEXA scans more often than every 2 years
4. Do not prescribe bisphosphonates for patients at low risk of fracture
5. Do not perform whole body bone scans (e.g. scintigraphy) for diagnostic screening for peripheral and axial arthritis in the adult population

Septic Arthritis
- for any acute monoarthritis or flare of pre-existing arthritis, one must rule out septic etiology; consider empiric antibiotic treatment until septic arthritis is excluded by history, physical exam, and synovial fluid analysis
- major bacteria are gram positive cocci (75-80%) especially S. aureus, and gram-negative bacilli (15-20%)
- poor prognostic factors: older age, immunocompromised, delay in treatment, previously damaged joint, joint prosthesis
- see Infectious Diseases for Gonococcal Arthritis, ID15 and Orthopedics, OR10

Septic arthritis is a medical emergency; it leads to rapid joint destruction, and there is a 10-15% risk of mortality
**Degenerative Arthritis: Osteoarthritis**

**Definition**
- progressive deterioration of articular cartilage and surrounding joint structures caused by genetic, metabolic, biochemical, and biomechanical factors with secondary components of inflammation

**Classification (based on etiology)**
- primary (idiopathic)
  - most common, unknown etiology
- secondary
  - post-traumatic or mechanical
  - post-inflammatory (e.g. RA) or post-infectious
  - heritable skeletal disorders (e.g. scoliosis)
  - endocrine disorders (e.g. acromegaly, hyperparathyroidism, hypothyroidism)
  - metabolic disorders (e.g. gout, pseudogout, hemochromatosis, Wilson’s disease, ochronosis)
  - neuropathic (e.g. Charcot joints)
  - atypical joint trauma due to peripheral neuropathy (e.g. DM, syphilis)
  - AVN
  - other (e.g. congenital malformation)

**Pathophysiology**
- the process appears to be initiated by abnormalities in biomechanical forces and/or, less often, in cartilage
- elevated production of pro-inflammatory cytokines is important in OA progression
- tissue catabolism > repair
- genetic, environmental, mechanical loading, age and gender factors contribute, but mechanism is unknown
- now considered to be a systemic musculoskeletal disorder rather than a focal disorder of synovial joints

**Epidemiology**
- most common arthropathy (accounts for ~75% of all arthritis)
- increased prevalence with increasing age (35% of 30 yr olds, 85% of 80 yr olds)

**Risk Factors**
- genetic predisposition, advanced age, obesity (for knee and hand OA), female, trauma

**Signs and Symptoms**
- localized to affected joints (not a systemic disease)
- pain is often insidious, gradually progressive, with intermittent flares and remissions, neuropathic pain may also be present
- fatigue, poor sleep, impact on mood (depression, anxiety)

<table>
<thead>
<tr>
<th>Signs</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint line tenderness; stress pain ± joint effusion</td>
<td>Joint pain with motion; relieved with rest</td>
</tr>
<tr>
<td>Bony enlargement at affected joints</td>
<td>Short duration of stiffness (&lt; 1/2 h) after immobility</td>
</tr>
<tr>
<td>Malalignment/deformity (angulation)</td>
<td>Joint instability/buckling</td>
</tr>
<tr>
<td>Limited ROM</td>
<td>Joint locking due to “joint mouse” (bone or cartilage fragment)</td>
</tr>
<tr>
<td>Crepitus on passive ROM</td>
<td>Loss of function or other internal derangements (e.g. meniscal tear)</td>
</tr>
<tr>
<td>Inflammation (mild if present)</td>
<td>*</td>
</tr>
<tr>
<td>Patiarticular muscle atrophy</td>
<td>*</td>
</tr>
</tbody>
</table>

**Joint Involvement**
- asymmetric (knees usually affected bilaterally)
- hand
  - DIP (Heberden’s nodes = osteophytes → enlargement of joints)
  - PIP (Bouchard’s nodes)
  - CMC (usually thumb squaring)
  - 1st MCP (other MCPs are usually spared)
- hip
  - usually presents as groin pain ± dull or sharp pain in the trochanteric area, internal rotation and abduction are lost first
  - pain can radiate to the anterior thigh, but generally does not go below the knee
- knee
  - initial narrowing of one compartment, medial > lateral; seen on standing x-rays, often patellar-femoral joint involved

**The Radiographic Hallmarks of OA**
- Joint space narrowing
- Subchondral sclerosis
- Subchondral cysts
- Osteophytes

**Obesity is linked to OA in the knee as well as CMC, which suggests a systemic inflammatory component to OA**

**Figure 3. Common sites of joint involvement in OA**
- Hand (DIP, PIP, 1st CMC)
- Hip
- Knee
- 1st MTP
- L-spine (L4-L5, L5-S1)
- C-spine
- Uncommon: ankle, shoulder, elbow, MCP, rest of wrist

**Figure 4. Hand findings in OA**
- OA of MCP joints can be seen in hemochromatosis or chondrocalcinosis
• foot
  - common in first MTP and midfoot
• lumbar spine
  - very common, especially L4-L5, L5-S1
  - degeneration of intervertebral discs and facet joints
• reactive bone growth can contribute to neurological impingement (e.g. sciatica, neurogenic claudication) or spondylolisthesis (forward or backward movement of one vertebra over another)
• cervical spine
  - commonly presents with neck pain that radiates to scapula, especially in mid-lower cervical area (C5 and C6)

Investigations
• blood work
  - normal CBC and ESR, CRP
  - negative RF and ANA
• radiology: 4 hallmark findings
• synovial fluid: non-inflammatory (see Table 8)

Treatment
• presently no treatment alters the natural history of OA
• prevention: prevent sports injury, healthy weight management
• non-pharmacological therapy
  - weight loss (minimum 5-10 lb loss) if overweight
  - physiotherapy: heat/cold, low impact exercise programs
  - occupational therapy: aids, splints, cane, walker, bracing
• pharmacological therapy (see Table 32)
  - oral: acetaminophen/NSAIDs, glucosamine ± chondroitin (nutraceuticals not proven)
  - treat neuropathic pain if present (anti-depressants, anti-epileptics, etc.)
  - joint injections: corticosteroid, hyaluronic acid (questionable benefit)
  - topical: capsaicin, NSAIDs
• surgical treatment
  - joint debridement, osteotomy, total and/or partial joint replacement, fusion
    (see Orthopedics, OR30)

Seropositive Rheumatic Disease
• diagnosis vs. classification in rheumatology
• diagnostic criteria are often dependent on disease progression and evolution over time, as early objective measures are often unavailable
• classification criteria are derived from studying patients with long-term diseases and clear diagnoses in order to determine which criteria have good specificity in the early prediction of certain diagnoses
• seropositive arthropathies are characterized by the presence of a serologic marker such as positive RF or ANA
• a small subset of the vasculitides, the small vessel ANCA-associated vasculitides, have a measurable serological component, but even these are often considered a separate entity from seropositive disease by experts
Table 10. Autoantibodies and their Prevalence in Rheumatic Diseases

<table>
<thead>
<tr>
<th>Autoantibody</th>
<th>Disease</th>
<th>Healthy Controls</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF</td>
<td>RA 80%</td>
<td>&lt;5%</td>
<td>RF directed against Fc domain of IgG. Sensitive in RA (can be negative early in disease course), levels correlate with disease activity. Present in most seropositive diseases. Non-specific; may be present in IE, TB, hepatitis C, silicosis, sarcoidosis.</td>
</tr>
<tr>
<td></td>
<td>SS 50%</td>
<td>10-20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SLE 20%</td>
<td>&gt;65</td>
<td></td>
</tr>
<tr>
<td>Anti-CCP</td>
<td>RA 80%</td>
<td>Specific for RA (94-98%)</td>
<td>May be useful in early disease and to predict aggressive disease.</td>
</tr>
<tr>
<td>ANA</td>
<td>SLE 98%</td>
<td>&lt;5%</td>
<td>Ab against nuclear components (DNA, RNA, histones, centromere). Sensitive but not specific for SLE. Given high false positive rate - only measure when high pre-test probability of CTD.</td>
</tr>
<tr>
<td></td>
<td>MCTD 100%</td>
<td>(seen in other CTDs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SS 40-70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CREST 60-80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-dsDNA</td>
<td>SLE 50-70%</td>
<td>0%</td>
<td>Specific for SLE (95%). Levels correlate with disease activity.</td>
</tr>
<tr>
<td>Anti-Sm</td>
<td>SLE &lt;30%</td>
<td>0%</td>
<td>Specific but not sensitive for SLE. Does not correlate with SLE disease activity.</td>
</tr>
<tr>
<td>Anti-Ro (SSA)</td>
<td>SS 40-95%</td>
<td>0.5%</td>
<td>Subacute cutaneous SLE (74%). May be only Ab present in ANA negative SLE. Increases risk of having child with neonatal lupus syndrome.</td>
</tr>
<tr>
<td></td>
<td>SSC 21%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SLE 32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RA 15%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-La (SSB)</td>
<td>SS 40%</td>
<td>0%</td>
<td>Usually occurs with anti-Ro. Specific for SS and SLE when anti-Ro is also positive. Increases risk of having child with neonatal lupus syndrome.</td>
</tr>
<tr>
<td></td>
<td>SLE 10%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid Ab (LAC, ACLA)</td>
<td>APLA 100%</td>
<td>&lt;5%</td>
<td>By definition present in APLA. Only small subset of SLE patients develop clinical syndrome of APLA. If positive, will often get a false positive VDRL test.</td>
</tr>
<tr>
<td></td>
<td>SLE 31-40%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-Histone</td>
<td>Drug-induced SLE 95%</td>
<td>0%</td>
<td>Highly specific for drug-induced SLE.</td>
</tr>
<tr>
<td></td>
<td>SLE 30-80%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-RNP</td>
<td>MCTD</td>
<td>0%</td>
<td>High titres present in MCTD; present in many other CTD (especially SLE).</td>
</tr>
<tr>
<td>Anti-Centromere</td>
<td>CREST &gt;80%</td>
<td>0%</td>
<td>Specific for CREST variant of systemic sclerosis.</td>
</tr>
<tr>
<td>Anti-Topoisomerase I (formerly Scl-70)</td>
<td>Diffuse SSc 26-76%</td>
<td>0%</td>
<td>Specific for SSc. Increased risk pulmonary fibrosis in SSc.</td>
</tr>
<tr>
<td>c-ANCA</td>
<td>Active GPA &gt;90%</td>
<td>0%</td>
<td>Specific and sensitive.</td>
</tr>
<tr>
<td>p-ANCA</td>
<td>GPA 10% Other vasculitis</td>
<td>0%</td>
<td>Nonspecific and poor sensitivity (found in ulcerative colitis, PAN, microscopic polyangiitis, Churg-Strauss, rapidly progressive glomerulonephritis).</td>
</tr>
<tr>
<td>Anti-Mi-2</td>
<td>DMM 15-20%</td>
<td>0%</td>
<td>Specific but not sensitive (not available in all centres).</td>
</tr>
<tr>
<td>Ab Against RBCs, WBCs, or Platelets</td>
<td>SLE</td>
<td>Perform direct Coomb's test Test Hb, reticulocyte, leukocyte and platelet count, antiplatelet Abs.</td>
<td></td>
</tr>
</tbody>
</table>

*note: some individuals in the normal population test positive for RF and/or ANA, but do not have the conditions listed in Table 10*
**Rheumatoid Arthritis**

**Definition**
- chronic, symmetric, erosive synovitis of peripheral joints (e.g. wrists, MCPs, MTPs)
- characterized by a number of extra-articular features

**Table 12. 2010 ACR/EULAR Classification Criteria for RA**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Score</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Joint involvement (swollen or tender)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Large joint (shoulders, elbows, hips, knees, and ankles)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2-10 large joints</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>1-3 small joints (MCPs, PIPs, wrists, 2nd-5th MTPs)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>&gt;4 small joints</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&gt;10 joints (at least 1 small joint)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Total score of ≥6: definite RA Must have ≥1 joint with definite clinical swelling, not better explained by other disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Serology Negative RF and negative Anti-CCP</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Low-positive RF or low-positive Anti-CCP (&lt;3x ULN)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>High-positive RF or high-positive Anti-CCP (&gt;3x ULN)</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>3. Acute phase reactants Normal CRP and normal ESR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Abnormal CRP and abnormal ESR</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4. Duration of symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6 wk</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>≥6 wk</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

RA is an independent risk factor for atherosclerosis and CV disease. RA is associated with increased overall mortality/morbidity from all causes: CV disease, neoplasm (especially lymphoma), infection.

**Common Presentation**
- Morning stiffness >1 h, improves with use
- Symmetric joint involvement
- Initially involves small joints of hands and feet
- Constitutional symptoms
Pathophysiology

- autoimmune disorder, unknown etiology
- complex interaction of genes and environment leading to breakdown of immune tolerance: many pathways result in autoreactivity leading to a final common pathway to synovial inflammation
  - genetic predisposition: HLA-DR4/DR1 association (93% of patients have either HLA type), cytokine promotors, T cell signaling
  - epigenetic: DNA hypomethylation, dysregulated histones, microRNA expression
  - environment: repeated activation of innate immunity, cigarette smoking increases susceptibility 20-40 fold
    - induction of enzymes that convert arginine to citrulline caused by environmental stress (cigarette smoking)
  - RA: propensity for immune reactivity to neoepitopes created by protein citrullination and production of anti-citrullinated protein antibodies
  - second-hit required for autoantibody-mediated synovial inflammation: increase in vascular permeability provides access to joint and permits complement fixation, recruitment of immune cells, and inflammation
- once inflammatory process is established, synovium organizes itself into an invasive tissue that degrades cartilage and bone
  - direct invasion of proliferating synovial fibroblast cells into cartilage at the pannus-cartilage junction; inflammatory mediators lead to release of collagenases resulting in destruction of articular cartilage and subchondral bone
  - fibroblast-like synoviocytes in the rheumatoid synovium can migrate from joint to joint (may explain symmetric polyarticular presentation)
- progressive bone destruction with absence of bone repair in response to inflammation
  - TNF increases osteoclasts and decreases osteoblasts at the site of inflammation
  - RANK ligand regulates osteoclast-mediated destruction

Epidemiology

- most common inflammatory arthritis: prevalence 1% of population
- F:M = 3:1
- age of onset 20-40 yr

Signs and Symptoms

- variable course of exacerbations and remissions
- morning stiffness >1 h, improves with use, increases with rest
- polyarthritis: symmetric joint involvement (tender, swollen), small joints affected, most commonly MCP, PIP, MTP
- extra-articular (systemic) symptoms: profound fatigue, depression, myalgia, weight loss
- limitation of function and decrease in global functional status
- complications of chronic synovitis
  - signs of mechanical joint damage: loss of motion, instability, deformity, crepitus, joint deformities
    - swan neck deformity, boutonnière deformity
    - ulnar deviation of MCP, radial deviation of wrist joint
    - hammer toe, mallet toe, claw toe
    - flexion contractures
  - atlanto-axial and subaxial subluxation
  - C-spine instability
  - neurological impingement (long tract signs)
  - difficult/dangerous intubation: risk of worsening subluxation and damage to spinal cord
  - limited shoulder mobility, spontaneous tears of the rotator cuff leading to chronic spasm
  - tenosynovitis → may cause rupture of tendons
  - carpal tunnel syndrome
  - ruptured Baker’s cyst (outpouching of synovium behind the knee); presentation similar to acute DVT

Table 13. Extra-Articular Features of RA Classified by Underlying Pathophysiology

<table>
<thead>
<tr>
<th>System</th>
<th>Vasculitic</th>
<th>Lymphocytic Infiltrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>Periungual infarction, cutaneous ulcers, palpable purpura</td>
<td>Rheumatoid nodules (may have vasculitic component)</td>
</tr>
<tr>
<td>Ocular</td>
<td>Episcleitis, scleritis</td>
<td>Keratoconjunctivitis sicca</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Xerostomia, Hashimoto’s thyroiditis</td>
<td>(see Endocrinology, E27)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Peri-/myocarditis, valvular disease, conduction defects</td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Pulmonary fibrosis, pleural effusion, pleuritis, pulmonary nodules</td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy: sensory stocking-glove, mononeuritis multiplex</td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>Splenomegaly, neutropenia (Felty’s syndrome)</td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td>Amyloidosis – caused by accumulation of abnormal proteins</td>
<td></td>
</tr>
</tbody>
</table>

Figure 5. Common sites of joint involvement in RA

Figure 6. Joint deformities

Syndromes in RA
- SS (common): keratoconjunctivitis sicca and xerostomia (dry eyes and mouth)
- Caplan’s syndrome (rare): multiple pulmonary nodules and pneumoconiosis
- Felty’s syndrome (rare): arthritis, splenomegaly, neutropenia
Classification of Global Functional Status in RA

- **Class I**: able to perform usual ADLs (self-care, vocational, avocational)
- **Class II**: able to perform self-care and vocational activities, restriction of avocational activities
- **Class III**: able to perform self-care, restriction of vocational and avocational activities
- **Class IV**: limited ability to perform self-care, vocational, and avocational activities

Investigations

- blood work
  - RF: sensitivity 80% but non-specific; may not be present at onset of symptoms; levels correlate with disease activity
  - can be associated with more erosions, more extra-articular manifestations, and worse function
  - anti-CCP: sensitivity 80% but more specific (94-98%); may precede onset of symptoms
  - increased disease activity is associated with decreased Hb (anemia of chronic disease), increased platelets, ESR, CRP, and RF
- imaging
  - x-rays may be normal at onset
  - first change is periarticular osteopenia, followed by erosions
  - U/S, MRI may be used to image hands to detect early synovitis and erosions

Treatment

- goals of therapy: remission or lowest possible disease activity
- control disease activity
- relieve pain and stiffness
- maintain function and lifestyle
- prevent or control joint damage
- key is early diagnosis and early intervention with DMARDs
- “window of opportunity” = early treatment within first 3 mo of disease may allow better control/remission
- behavioural
  - exercise program (isometrics and active, gentle ROM exercise during flares, aquatic/aerobic/strengthening exercise between flares), assistive devices as needed
- job modification may be necessary
- pharmacologic: alter disease progression
  - DMARDs
    - Standard of care and should be started as soon as possible
    - MTX is the gold standard and is first-line unless contraindicated
      - delayed onset of action (may take 8-12 wks)
      - potential toxicities: GI, hematologic, hepatic, pulmonary, teratogenic
      - if inadequate response (3-6 mo) → combine or switch
      - add-ons include: hydroxychloroquine, sulfasalazine, leflunomide
  - biologics
    - indicated if inadequate response to DMARDs
    - can be combined with DMARD therapy
    - options: infliximab, etanercept, adalimumab, abatacept, rituximab, tocilizumab
    - reassess every 3-6 mo and monitor disease severity
- pharmacologic: reduce inflammation and pain
  - NSAIDs
    - individualize according to efficacy and tolerability
    - contraindicated/cautioned in some patients (e.g. PUD, ischemic cardiac disease, pregnancy)
    - add acetaminophen ± opioid prn for synergistic pain control
  - corticosteroids
    - local: injections to control symptoms in a specific joint
    - systemic (prednisone)
      - low dose (5-10 mg/d) useful for short-term to improve symptoms if NSAIDs ineffective, to bridge gap until DMARDs take effect
      - severe RA: add low dose prednisone to DMARDs
      - do baseline DEXA bone density scan and consider bone supportive pharmacologic therapy if using corticosteroids >3 mo at 7.5mg/d
      - cautions/contraindications: active infection, TB, osteoporosis, HTN, gastric ulcer, DM

Follow-Up Management and Clinical Outcomes

- follow-up every 3-6 mo, then 6-12 mo after inflammation has been suppressed
- examine joints for active inflammation – if active, consider adjusting medications, PT/OT
- if assessment reveals joint damage – consider analgesia, referral to PT/OT, surgical options
- outcome depends on disease activity, joint damage, physical functional status, psychological health, and comorbidities

Conclusions

- Initial combination therapy with prednisone or infliximab results in faster response rates. Whether faster initial response rates leads to better long-term disease outcomes has not yet been studied.

Comparison of Treatment Strategies in Early Rheumatoid Arthritis

- **Rheumatoid Arthritis**
- **Classification of Global Functional Status in RA**
- **Investigations**
- **Treatment**
- **Follow-Up Management and Clinical Outcomes**
- **Conclusions**

- Poor prognostic features of RA include: young age of onset, high RF titer, elevated ESR, activity of >20 joints, and presence of extra-articular features

- Only DMARDs and biologics (not analgesics or NSAIDs) after the course of RA

- Standard of care and should be started as soon as possible

- **Side Effects of Steroids**
  - Weight gain
  - Osteoporosis
  - AVN
  - Cataracts, glaucoma
  - PUD
  - Susceptibility to infection
  - Easy bruising
  - Acne
  - HTN
  - Hyperlipidemia
  - Hypokalemia, hyperglycemia
  - Mood swings

- **Comparison of Treatment Strategies in Early Rheumatoid Arthritis**
  - **Rheumatoid Arthritis**
  - **Classification of Global Functional Status in RA**
  - **Investigations**
  - **Treatment**
  - **Follow-Up Management and Clinical Outcomes**
  - **Conclusions**

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  - Weight gain
  - Osteoporosis
  - AVN
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  - PUD
  - Susceptibility to infection
  - Easy bruising
  - Acne
  - HTN
  - Hyperlipidemia
  - Hypokalemia, hyperglycemia
  - Mood swings

- Only DMARDs and biologics (not analgesics or NSAIDs) after the course of RA
• functional capacity is a useful tool for determining therapeutic effectiveness: many tools for evaluation have been validated
• patients with RA have an increased prevalence of other serious illnesses: infection (e.g. pulmonary, skin, joint), renal impairment, lymphoproliferative disorders, cardiovascular disease (correlates with disease activity and duration)
• increased risk of premature mortality, decreased life expectancy (most mortality not directly caused by RA)

Surgical Therapy
• indicated for structural joint damage
• surgical options include: synovectomy, joint replacement, joint fusion, reconstruction/tendon repair

Systemic Lupus Erythematosus

• see Nephrology, NP22 and Dermatology, D41

Definition
• chronic inflammatory multi-system disease of unknown etiology
• characterized by production of autoantibodies and diverse clinical manifestations

Table 14. Diagnostic Criteria of SLE*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td>Malar rash Classic “butterfly rash”, sparing of nasolabial folds, no scarring</td>
</tr>
<tr>
<td></td>
<td>Discoid rash May cause scarring due to invasion of basement membrane</td>
</tr>
<tr>
<td></td>
<td>Photosensitivity Skin rash in reaction to sunlight</td>
</tr>
<tr>
<td></td>
<td>Oral/nasal ulcers Usually painless</td>
</tr>
<tr>
<td></td>
<td>Arthritis Symmetric, involving ≥2 small or large peripheral joints, non-erosive</td>
</tr>
<tr>
<td></td>
<td>Serositis Pleuritis or pericarditis</td>
</tr>
<tr>
<td></td>
<td>Neurologic disorder Seizures or psychosis</td>
</tr>
<tr>
<td>LABORATORY</td>
<td>Renal disorder Proteinuria (&gt;0.5 g/d or 3+), cellular casts (RBC, Hb, granular, tubular, mixed)</td>
</tr>
<tr>
<td></td>
<td>Hematologic disorder Hemolytic anemia, leukopenia, lymphopenia, thrombocytopenia</td>
</tr>
<tr>
<td></td>
<td>Immunologic disorder Anti-dsDNA or anti-Sm or antiphospholipid Ab (anticardiolipin Ab, SLE anticoagulant) or false positive VDRL with 6 mo confirmatory negative</td>
</tr>
<tr>
<td></td>
<td>ANA Most sensitive test (98%), not specific</td>
</tr>
</tbody>
</table>

*Note: “4, 7, 11” rule → 4 (or more) out of 11 criteria (4 lab, 7 clinical) must be present, serially or simultaneously, for diagnosis

Etiology and Pathophysiology
• production of autoantibodies causing multi-organ inflammation
• multi-factorial etiology
• genetics
  • common association with HLA-B8/DR3: ~10% have positive family history
  • strong association with defects in apoptotic clearance → fragments of nuclear particles captured by antigen-presenting cells → develop anti-nuclear antibodies
  • cytokines involved in inflammatory process and tissue injury: B-lymphocyte stimulator (BlyS), IL-6, IL-17, IL-18, TNF-α
• environment
  • UV radiation, cigarette smoking, infection, vitamin D deficiency
  • estrogen
  • increased incidence after puberty, decreased incidence after menopause
  • men with SLE have higher concentration of estrogenic metabolites
• infection
  • viral (non-specific stimulant of immune response)
• drug-induced
  • anti-hypertensives (hydralazine), anti-convulsants (phenytoin), anti-arrhythmics (propranolol), isoniazid, biologics, oral contraceptive pills
  • anti-histone Ab are commonly seen in drug-induced SLE
  • symptoms resolve with discontinuation of offending drug
Epidemiology
- prevalence: 0.05% overall
- F:M = 10:1
- age of onset in reproductive yr (13-40)
- more common and severe in African-Americans and Asians
- bimodal mortality pattern
  - early (within 2 yr)
    - active SLE, active nephritis, infection secondary to steroid use
  - late (>10 yr)
    - inactive SLE, inactive nephritis, atherosclerosis likely due to chronic inflammation

Signs and Symptoms
- characterized by periods of exacerbation and remission

Table 15. Symptoms of SLE

<table>
<thead>
<tr>
<th>System</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic</td>
<td>Fatigue, malaise, weight loss, fever, lymphadenopathy</td>
</tr>
<tr>
<td>Renal</td>
<td>HTN, peripheral edema, glomerulonephritis, renal failure</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Photosensitivity, malar rash, discoid rash, oral ulcers, alopecia (hair loss), purpura, panniculitis (inflammation of subcutaneous fat and muscle tissue), urticaria</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Polyradialgia, polyarthritis, myalgias, AVN; reducible deformities of hand = Jaccoud's arthritis</td>
</tr>
<tr>
<td>Ophthalmic</td>
<td>Keratoconjunctivitis sicca, episcleritis, scleritis, cystoid bodies (cotton wool exudates on fundoscopy = infarction of nerve cell layer of retina)</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Pericarditis, CAD, non-bacterial endocarditis (Libman-Sachs), myocarditis</td>
</tr>
<tr>
<td>Vascular</td>
<td>Raynaud’s phenomenon, livedo reticularis (mottled discoloration of skin due to narrowing of blood vessels, characteristic lacy or net-like appearance), thrombosis, vasculitis</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pleuritis, ILD, pulmonary HTN, PE, alveolar hemorrhage</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Pancreatitis, SLE enteropathy, hepatitis, hepatomegaly, splenomegaly</td>
</tr>
<tr>
<td>Neurologic</td>
<td>H/A, depression, psychosis, seizures, cerebritis, transverse myelitis, peripheral neuropathy, stroke</td>
</tr>
<tr>
<td>Life/Organ-Threatening</td>
<td>Cardiac: coronary vasculitis, malignant HTN, tamponade</td>
</tr>
<tr>
<td></td>
<td>Hematologic: hemolytic anemia, neutropenia, thrombocytopenia, TTP, thrombosis</td>
</tr>
<tr>
<td></td>
<td>Neurologic: seizures, CVA, stroke</td>
</tr>
<tr>
<td></td>
<td>Respiratory: pulmonary hypertension, pulmonary hemorrhage, emboli</td>
</tr>
</tbody>
</table>

Investigations
- ANA (sensitivity 98%, but poor specificity → used as a screening test, ANA titres are not useful to follow disease course)
- anti-dsDNA and anti-Sm are specific (95-99%)
- anti-dsDNA titer and serum complement (C3, C4) are useful to monitor treatment response in patients who are clinically and serologically concordant
  - anti-dsDNA increases and C3 and C4 decrease with disease activity
- antiphospholipid Ab (anti-cardiolipin Ab and SLE anticoagulant), may cause increased risk of clotting and increased aPTT

Treatment
- goals of therapy
  - treat early and avoid long-term steroid use, if unavoidable see Endocrinology, E42 for osteoporosis management
  - if high doses of steroids necessary for long-term control, add steroid-sparing agents and taper when possible
  - treatment is tailored to organ system involved and severity of disease
  - all medications used to treat SLE require periodic monitoring for potential toxicity
- dermatologic
  - sunscreen, avoid UV light and estrogens
  - topical steroids, hydroxychloroquine
- musculoskeletal
  - NSAIDs ± gastroprotective agent for arthritis (also beneficial for pleuritis and pericarditis)
  - hydroxychloroquine improves long-term control and prevents flares
  - bisphosphonates, calcium, vitamin D to combat osteoporosis
- organ-threatening disease
  - high-dose oral prednisone or IV methylprednisolone in severe disease
  - steroid-sparing agents: azathioprine, MTX, mycophenolate mofetil
  - IV cyclophosphamide for serious organ involvement (e.g. cerebritis or lupus nephritis) see Nephrology, NP22 for clinical features of lupus nephritis

Drug-Induced SLE
Often presents atypically with systemic features and serositis; usually associated with anti-histone Ab

Raynaud’s Phenomenon
Vasospastic disorder characteristically causing discoloration of fingers and toes (white → blue → red). Classic triggers: cold and emotional stress

Radiographically, the arthritis of SLE is non-erosive (unlike RA)

Consider SLE in a patient who has involvement of 2 or more organ systems
Antiphospholipid Antibody Syndrome

Definition
- multi-system vasculopathy manifested by recurrent thromboembolic events, spontaneous abortions, and thrombocytopenia
- often presents with migraine-type H/As
- circulating antiphospholipid autoantibodies interfere with coagulation cascade
- primary APLA: occurs in the absence of other disease
- secondary APLA: occurs in the setting of a connective tissue disease (including SLE), malignancy, drugs (hydralazine, procainamide, phenytoin, interferon, quinidine), and infections (HIV, TB, hepatitis C, infectious mononucleosis)
- catastrophic APLA: development within 1 wk of small vessel thrombotic occlusion in ≥3 organ systems with positive antiphospholipid Ab (high mortality)

Table 16. Classification Criteria of APLA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>CLINICAL</td>
<td>Vascular thrombosis&lt;br&gt;Arterial: stroke/TIA, multi-infarct dementia, MI, valvular incompetence, limb ischemia&lt;br&gt;Venous: DVT, PE, renal and retinal vein thrombosis&lt;br&gt;Must be confirmed by imaging or histopathology&lt;br&gt;Pregnancy morbidity&lt;br&gt;Fetal death (&gt;10 wk GA), recurrent spontaneous abortions (&lt;10 wk GA) or premature birth (&lt;34 wk GA)</td>
</tr>
<tr>
<td>LABORATORY</td>
<td>SLE anticoagulant&lt;br&gt;Anti-cardiolipin Ab IgG and/or IgM&lt;br&gt;Anti-β2 glycoprotein I Ab IgG and/or IgM</td>
</tr>
</tbody>
</table>

* 1 clinical and 1 laboratory criteria must be present

Signs and Symptoms
- see clinical criteria in Table 16
- hematologic
  - thrombocytopenia, hemolytic anemia, neutropenia
- dermatologic
  - livedo reticularis, Raynaud's phenomenon, purpura, leg ulcers, and gangrene

Treatment
- thrombosis
  - lifelong anti-coagulation with warfarin
  - target INR 2.0-3.0 for first venous event, >3.0 for recurrent and/or arterial event
- recurrent fetal loss
  - heparin/low molecular weight heparin ± ASA during pregnancy
- catastrophic APLA
  - high-dose steroids, anti-coagulation, cyclophosphamide, plasmapheresis

Scleroderma (i.e. Systemic Sclerosis)

Definition
- a non-inflammatory autoimmune disorder characterized by widespread small vessel vasculopathy, production of autoantibodies, and fibroblast dysfunction causing fibrosis

Figure 8. Forms of scleroderma
Table 17. The American College of Rheumatology (ACR)/European League Against Rheumatism (EULAR) Criteria for Scleroderma*  

<table>
<thead>
<tr>
<th>Item</th>
<th>Sub-item</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Skin thickening of fingers of both hands extending proximal to the MTPs (sufficient criterion)</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>2. Skin thickening of the fingers</td>
<td>Puffy fingers</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sclerodactyly</td>
<td>4</td>
</tr>
<tr>
<td>3. Fingertip lesions</td>
<td>Digital tip ulcers</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Fingertip pitting scars</td>
<td>3</td>
</tr>
<tr>
<td>4. Telangiectasia</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>5. Abnormal nailfold capillaries</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>6. Pulmonary arterial HTN ± ILD (max score 2)</td>
<td>Pulmonary arterial HTN</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>ILD</td>
<td>2</td>
</tr>
<tr>
<td>7. Raynaud’s phenomenon</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>8. Scleroderma related Ab</td>
<td>Anticentromere</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Anti-topoisomerase I</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anti-RNA polymerase III</td>
<td></td>
</tr>
</tbody>
</table>

* Score of ≥9 is sufficient to classify a patient as having definite scleroderma (sensitivity 0.95, specificity 0.93)  
Arthritis & Rheum 2013;65(11):2737-2747  

Etiology and Pathophysiology  
• idiopathic vasculopathy (not vasculitis) leading to atrophy and fibrosis of tissues  
  • intimal proliferation and media mucinous degeneration → progressive obliteration of vessel lumen → fibrotic tissue  
  • resembles malignant HTN  

Epidemiology  
• F:M = 3-4:1, peaking in 5th and 6th decades  
• associated with HLA-DR1  
• associated with environmental exposure (silica, epoxy resins, toxic oil, aromatic hydrocarbons, polyvinyl chloride)  
• limited systemic sclerosis has a higher survival prognosis (>70% at 10 yr) than diffuse systemic sclerosis (40-60% at 10 yr)  

Signs and Symptoms  
Table 18. Clinical Manifestations of Scleroderma  

<table>
<thead>
<tr>
<th>System</th>
<th>Features</th>
</tr>
</thead>
</table>
| Dermatologic | Painless non-pitting edema → skin tightening  
Ulcations, calcinosis, periungual erythema, hypo/hyperpigmentation, pruritus, telangiectasias  
Characteristic face: mask-like facies with tight lips, beak nose, radial perioral furrows |
| Vascular | Raynaud’s phenomenon → digital pust, gangrene |
| Gastrointestinal (~90%) | Distal esophageal hypomotility → dysphagia  
Loss of lower esophageal sphincter function → GERD, ulcerations, strictures  
Small bowel hypomotility → bacterial overgrowth, diarrhea, bloating, cramps, malabsorption, weight loss  
Large bowel hypomotility → wide mouth diverticuli are pathognomonic radiographic finding on barium study |
| Renal | Mild proteinuria, Cr elevation, HTN  
“Scleroderma renal crisis” (10-15%) may lead to malignant arterial HTN, oliguria, and microangiopathic hemolytic anemia |
| Pulmonary | Interstitial fibrosis, pulmonary HTN, pleurisy, pleural effusions |
| Cardiac | Left ventricular dysfunction, pericarditis, pericardial effusion, arrhythmias |
| Musculoskeletal | Polyarthritis  
“Resorption of distal tufts” (radiological finding)  
Proximal weakness 2° to disuse, atrophy, low grade myopathy |
| Endocrine | Hypothyroidism |

Investigations  
• blood work  
  • CBC, Cr, ANA  
  • anti-topoisomerase 1/anti-Scl-70: specific but not sensitive for diffuse systemic sclerosis  
  • anti-centromere: favours diagnosis of CREST (limited systemic sclerosis)  
• PFT  
  • assess for interstitial lung disease  
• imaging  
  • CXR for fibrosis, echo for pulmonary HTN  

Scleroderma is the most common cause of secondary Raynaud’s phenomenon  
Lung disease is the most common cause of morbidity and mortality  
Raynaud’s Phenomenon DDx  
COLD HAND  
Cryoglobulins/Cryofibrinogens  
Obstruction/Occupational  
Lupus erythematosus, other connective tissue disease  
Diabetes mellitus/Drugs  
Hematologic problems (polycythemia, leukemia, etc.)  
Arterial problems (atherosclerosis)/  
Anorexia nervosa  
Neurologic problems (vascular tone)  
Disease of unknown origin (idiopathic)  
Features of Pathologic Raynaud’s Syndrome  
• New onset  
• Asymmetric  
• Precipitated by stimuli other than cold or emotion  
• Associated with distal pulp pitting or tissue reabsorption  
• Digit ischemia  
• Capillary dilatation by capillaroscopy
**Treatment**

- **dermatologic**
  - good skin hygiene
  - low-dose prednisone (>20 mg may provoke renal crisis if susceptible), MTX (limited evidence)
- **vascular**
  - patient education on cold avoidance
  - vasodilators (CCBs, local nitroglycerine cream, systemic PGE₂ inhibitors, PDE5 inhibitors)
- **gastrointestinal**
  - GERD: PPIs are first line, then H₂-receptor agonists
  - small bowel bacterial overgrowth: broad spectrum antibiotics (tetracycline, metronidazole)
- **renal disease**
  - ACEI for hypertensive crisis
  - see Nephrology, NP31 for scleroderma renal crisis
- **pulmonary**
  - early interstitial disease: cyclophosphamide
  - pulmonary HTN: vasodilators e.g. bosentan (Tracleer®), epoprostenol (Flolan®), PDE5 inhibitors
- **cardiac**
  - pericarditis: systemic steroids
- **musculoskeletal**
  - arthritis: NSAIDs
  - myositis: systemic steroids

---

**Idiopathic Inflammatory Myopathy**

**Definition**

- autoimmune diseases characterized by proximal muscle weakness = pain
- muscle becomes damaged by a non-suppurative lymphocytic inflammatory process

**Classification**

- **PM/DMM**
  - adult and juvenile form
  - associated with malignancy
    - increased risk of malignancy: age >50, DMM>PM, normal CK, refractory disease
    - 2.4-6.5 fold increased risk of underlying malignancy usually in internal organs
  - associated with other connective tissue disease, Raynaud’s phenomenon, autoimmune disorders

**Inclusion Body Myositis**

- age >50, M>F, slowly progressive, vacuoles in cells on biopsy
- suspect when patient unresponsive to treatment
- distal as well as proximal muscle weakness
- muscle biopsy positive for inclusion bodies

**POLYMYOSITIS/DERMATOMYOSITIS**

**Table 19. Classification Criteria for PM/DMM**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Symmetric proximal muscle weakness</td>
<td>Typical involvement of shoulder girdle and hip girdle</td>
</tr>
<tr>
<td>2. Elevated muscle enzymes</td>
<td>↑ CK, aldolase, LDH, AST, ALT</td>
</tr>
<tr>
<td>3. EMG changes</td>
<td>Short polyphasic motor units, high frequency repetitive discharge, insertional irritability</td>
</tr>
<tr>
<td>4. Muscle biopsy</td>
<td>Segmental fibre necrosis, basophilic regeneration, perivascular inflammation (DMM), endomysial inflammation (PM) and atrophy</td>
</tr>
<tr>
<td>5. Typical rash of dermatomyositis</td>
<td>Required for diagnosis of DMM (see below)</td>
</tr>
</tbody>
</table>

*Definite if 4 present, probable if 3 present*  
NEJM 1975;292:403-407

**Etiology and Pathophysiology**

- PM is CD8 cell-mediated muscle necrosis, found in adults
- DMM is B-cell and CD4 immune complex-mediated peri-fascicular vascular abnormalities

**Signs and Symptoms**

- progressive symmetrical proximal muscle weakness (shoulder and hip) developing over weeks to months
  - difficulty lifting head off pillow, arising from chair, climbing stairs
- dermatological
  - DMM has characteristic dermatological features (F>M, children and adults)
    - Gottron’s papules
      - pink-violaceous, flat-topped papules overlying the dorsal surface of the interphalangeal joints
    - Gottron’s sign

Signs of DMM
Gottron’s papules and Gottron’s sign are pathognomonic of DMM (occur in 70% of patients)

---

Malignancies Associated with DMM
- Breast
- Lung
- Colon
- Ovarian
• Gottron’s sign
  – erythematous, smooth or scaly patches over the dorsal IPs, MCPs, elbows, knees, or medial malleoli
• heliotrope rash: violaceous rash over the eyelids; usually with edema
• shawl sign: poikilodermatous erythematous rash over neck, upper chest, and shoulders
• mechanic’s hands: dark, dry, thick scale on palmar and lateral surface of digits
• periungual erythema

• cardiac
  – arrhythmias, CHF, conduction defect, ventricular hypertrophy, pericarditis
• gastrointestinal
  – oropharyngeal and lower esophageal dysphagia, reflux
• pulmonary
  – weakness of respiratory muscles, ILD, aspiration pneumonia

Investigations
• blood work: CK, ANA, anti-Jo-1 (DMM), anti-Mi-2, anti-SRP
• imaging: MRI may be used to localize biopsy site
• EMG, muscle biopsy

Treatment
• non-pharmacological treatment
  – physical therapy and occupational therapy
• pharmacological treatment
  – high-dose corticosteroid (1-2 mg/kg/d) and slow taper
  – add immunosuppressive agents (azathioprine, MTX, cyclosporine)
  – IVIg if severe or refractory
  – hydroxychloroquine for DMM rash
• malignancy surveillance
  – detailed history and physical (breast, pelvic, and rectal exam)
  – CXR, abdominal and pelvic U/S, fecal occult blood, Pap test, mammogram ± CT scan (thoracic, abdominal, pelvic)

Sjögren’s Syndrome

Definition
• autoimmune condition characterized by dry eyes (keratoconjunctivitis sicca/xerophthalmia) and dry mouth (xerostomia), caused by lymphocytic infiltration of salivary and lacrimal glands
• may evolve into systemic disorder with diminished exocrine gland activity in respiratory tract and skin
• primary and secondary form (associated with RA, SLE, DMM, and HIV)
• incidence estimated at 4/100,000 people
• 90% of cases are among females
• mean age of diagnosis is 40-60 yr

Table 20. American College of Rheumatology Classification for Sjögren’s*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Positive serum anti-SSA/Ro and/or anti-SSB/</td>
<td>La gr positive RF and ANA titer&gt;1:320</td>
</tr>
<tr>
<td>2. Labial salivary gland biopsy with focal lymphocytic sialadenitis with focus score ≥1 focus 4/mm²</td>
<td>Focus scores are histopathologic grading systems</td>
</tr>
<tr>
<td>3. Keratoconjunctivitis sicca with ocular staining score &gt;3</td>
<td>Orificial staining score based on fluorescein dye examination of conjunctiva and cornea to determine clinical changes</td>
</tr>
</tbody>
</table>

*Sjögren’s criteria is met in patients with signs/symptoms of Sjögren’s, who have at least 2 of the above features

Signs and Symptoms
• “sicca complex”: dry eyes (keratoconjunctivitis sicca/xerophthalmia), dry mouth (xerostomia)
• staphylococcal blepharitis
• dental caries, oral candidiasis, angular cheilitis (inflammation and fissuring at the labial commissures of the mouth)
• systemic complications
  – sinustis
  – autoimmune thyroid dysfunction
  – arthralgias, arthritis
  – subclinical diffuse ILD, xerotrachea leading to chronic dry cough
  – renal disease, glomerulonephritis
  – palpable purpura, vasculitis
  – peripheral neuropathy
• lymphoma risk greatly increased

Treatment
• ocular
  – artificial tears or surgical punctal occlusion for dry eyes
• oral
  - good dental hygiene, hydration
  - parasympathomimetic agents that stimulate salivary flow (e.g. pilocarpine)
  - topical nystatin or clotrimazole x 4-6 wk for oral candidiasis
• systemic
  - e.g. hydroxychloroquine, corticosteroids

**Mixed Connective Tissue Disease**

• syndrome with features of 3 different connective tissue diseases (e.g. SLE, scleroderma, PM)
• common symptoms: Raynaud’s phenomenon, swollen fingers
• blood work: anti-RNP (see Table 10)
• treatment is generally guided by the severity of symptoms and organ system involvement
• prognosis
  - 50-60% will evolve into SLE
  - 40% will evolve into scleroderma
  - only 10% will remain as MCTD for the rest of their lives
  - cardiac involvement (arrhythmia) common, renal or lung involvement rare

**Overlap Syndrome**

• syndrome with sufficient diagnostic features of 2+ different connective tissue diseases

**Vasculitides**

• inflammation and subsequent necrosis of blood vessels leading to tissue ischemia or infarction
• any organ system can be involved
• keys to diagnosis
  - clinical suspicion: suspect in cases of unexplained multiple organ ischemia or systemic illness with no evidence of malignancy or infection
  - labs non-specific: anemia, increased WBC and ESR, abnormal U/A
  - biopsy if tissue accessible
  - angiography if tissue inaccessible
• treatment generally involves corticosteroids and/or immunosuppressive agents

**Table 21. Classification of Vasculitis and Characteristic Features**

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMALL VESSEL</td>
<td></td>
</tr>
<tr>
<td>• Non-ANCA-associated</td>
<td>Immune complex-mediated (most common mechanism)</td>
</tr>
<tr>
<td>Predominantly cutaneous vasculitis</td>
<td>Also known as hypersensitivity/leukocytoclastic vasculitis</td>
</tr>
<tr>
<td>Henoch-Schönlein purpura (see Pediatrics, P94)</td>
<td>Vascular deposition of IgA causing systemic vasculitis (skin, GI, renal), usually self-limiting; most common in childhood</td>
</tr>
<tr>
<td>Essential cryoglobulinemic vasculitis</td>
<td>Systemic vasculitis caused by circulating cryoproteins forming immune complexes; may be associated with underlying infection (e.g. hepatitis C) or connective tissue disease</td>
</tr>
<tr>
<td>• ANCA-associated</td>
<td>Granulomatous inflammation of vessels of respiratory tract and kidneys, initially have URTI symptoms; most common in middle age</td>
</tr>
<tr>
<td>Granulomatosis with polyangitis (GPA, formerly Wegener’s) pR3 (c-ANCA) &gt; MPO (p-ANCA)</td>
<td>Granulomatous inflammation of vessels with hyperesosinophilia and eosinophilic tissue infiltration, frequent lung involvement (asthma, allergic rhinitis), can be associated with MPO or pR3, other manifestations include coronary arteritis, myocarditis and neuropathy, average age 40s</td>
</tr>
<tr>
<td>Eosinophilic granulomatosis with polyangitis (Churg-Strauss syndrome) (50% ANCA positive)</td>
<td>Microangiopathic polyangitis (70% ANCA positive, usually MPO) Pauci-immune necrotizing vasculitis, affecting kidneys (necrotizing glomerulonephritis), lungs (capillaritis and alveolar hemorrhage), skin, most common in middle age</td>
</tr>
<tr>
<td>MEDIUM VESSEL</td>
<td>Segmental, non-granulomatous necrotizing inflammation Unknown etiology in most cases, any age (average 40-50s), M&gt;F</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>Kawasaki disease (see Pediatrics, P94) Arteritis and mucocutaneous lymph node syndrome</td>
</tr>
</tbody>
</table>

**Features of Small Vessel Vasculitis**
- Palpable purpura
- Vesicles
- Chronic urticaria
- Superficial ulcers

**Features of Medium Vessel Vasculitis**
- Livedo reticularis
- Erythema nodosum
- Raynaud’s phenomenon
- Nodules
- Digital infarcts
- Ulcers
Table 21. Classification of Vasculitis and Characteristic Features (continued)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Characteristic Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>LARGE VESSEL</td>
<td></td>
</tr>
<tr>
<td>GCA/Temporal arteritis</td>
<td>Inflammation predominantly of the aorta and its branches</td>
</tr>
<tr>
<td>&gt;50 yr of age, F&gt;M</td>
<td></td>
</tr>
<tr>
<td>Takayasu’s arteritis</td>
<td>“Pulseless disease”, unequal peripheral pulses, chronic inflammation, most</td>
</tr>
<tr>
<td></td>
<td>often the aorta and its branches</td>
</tr>
<tr>
<td></td>
<td>Usually young adults of Asian descent, F&gt;M; risk of aortic aneurysm</td>
</tr>
<tr>
<td>OTHER VASCULITIDES</td>
<td></td>
</tr>
<tr>
<td>Buerger’s disease (‘Thromboangiitis Obliterans’)</td>
<td>Inflammation secondary to pathological clotting, affects small and medium-sized vessels of distal extremities, may lead to distal claudication and gangrene, most important etiologic factor is cigarette smoking</td>
</tr>
<tr>
<td></td>
<td>Most common in young Asian males</td>
</tr>
<tr>
<td>Behçet’s disease</td>
<td>Leukocytoclastic vasculitis, multi-system disorder presenting with ocular</td>
</tr>
<tr>
<td></td>
<td>involvement (uveitis), recurrent oral and genital ulceration, venous thrombosis,</td>
</tr>
<tr>
<td></td>
<td>skin and joint involvement, more common in Mediterranean and Asia, average age 30 yr</td>
</tr>
<tr>
<td></td>
<td>old, M&gt;F</td>
</tr>
<tr>
<td>Vasculitis mimicry (i.e. pseudo-vasculitis)</td>
<td>Cholesterol emboli, atrial myxoma</td>
</tr>
</tbody>
</table>

Figure 9. Classification of vasculitides by vessel size

Small Vessel Non-ANCA Associated Vasculitis

CUTANEOUS VASCULITIS
- subdivided into
  - drug-induced vasculitis
  - serum sickness reaction
  - vasculitis associated with other underlying primary diseases

Etiology and Pathophysiology
- cutaneous vasculitis following
  - drug exposure (allopurinol, gold, sulfonamides, penicillin, phenytoin)
  - viral or bacterial infection
  - idiopathic causes
- small vessels involved (post-capillary venules most frequently)
- usually causes a leukocytoclastic vasculitis: debris from neutrophils around vessels
- sometimes due to cryoglobulins which precipitate in cold temperatures

Signs and Symptoms
- palpable purpura ± vesicles and ulceration, urticaria, macules, papules, bullae, subcutaneous nodules
- renal or joint involvement may occur, especially in children

Investigations
- vascular involvement (both arteriole and venule) established by skin biopsy

Treatment
- stop possible offending drug
- corticosteroids ± immunosuppressive agents
- usually self-limiting
Small Vessel ANCA-Associated Vasculitis

GRANULOMATOSIS WITH POLYANGIITIS
(GPA, formerly known as Wegener’s Granulomatosis)

Definition
• granulomatous inflammation of vessels that may affect the upper airways (rhinitis, sinusitis), lungs (pulmonary nodules, infiltrates), and kidneys (glomerulonephritis, renal failure)
• highly associated with c-ANCA
• incidence 5 per 100,000; more common in Northern latitudes

Table 22. Classification Criteria for GPA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Nasal or oral involvement</td>
<td>Inflammation, ulcers, epistaxis</td>
</tr>
<tr>
<td>2. Abnormal findings on CXR</td>
<td>Nodules, cavitations, etc.</td>
</tr>
<tr>
<td>3. Urinary sediment</td>
<td>Microscopic hematuria ± RBC casts</td>
</tr>
<tr>
<td>4. Biopsy of involved tissue</td>
<td>Lungs show granulomas, kidneys show necrotizing segmental glomerulonephritis</td>
</tr>
</tbody>
</table>

*Diagnosed if 2 or more of the above 4 criteria present American College of Rheumatology, 1990

Etiology
• pathogenesis depends on genetic susceptibility and environmental triggers (e.g. infection)
  ▪ dysregulated immune response due to loss of B and T-cell tolerance
  ▪ acute vascular injury mediated by neutrophils and monocytes

Signs and Symptoms
• systemic
  ▪ malaise, fever, weakness, weight loss
• HEENT
  ▪ sinusitis or rhinitis, nasal crusting and bloody nasal discharge, nasoseptal perforation, saddle nose deformity
  ▪ proptosis due to: inflammation/vasculitis involving extra-ocular muscles, granulomatous retroorbital space occupying lesions or direct extension of masses from the upper respiratory tract
  ▪ hearing loss due to involvement of CN VIII
• pulmonary
  ▪ cough, hemoptysis, granulomatous upper respiratory tract masses
• renal
  ▪ hematuria
• other
  ▪ joint, skin, eye complaints, vasculitic neuropathy

Investigations
• blood work: anemia (normal MCV), increased WBC, increased Cr, increased ESR, elevated platelet count, ANCA (PR3 > MPO)
• urinalysis: proteinuria, hematuria, RBC casts
• CXR: pneumonitis, lung nodules, infiltrations, cavitary lesions
• biopsy: renal (segmental necrotizing glomerulonephritis), lung (granulomas, tracheobronchial erosion)
• c-ANCA and ESR often correlate with disease activity and used to monitor response to treatment in some patients

Treatment
• prednisone 1 mg/kg/d PO ± cyclophosphamide 2 mg/kg/d PO for 3-6 mo followed by high dose MTX (20-25 mg PO/SC weekly) or azathioprine (2 mg/kg/d PO OD)
• consider biologic agents (rituximab, IVIg) and plasmapheresis (PEXIVAS trial)

Medium Vessel Vasculitis

POLYARTERITIS NODOSA

Definition
• systemic, necrotizing vasculitis of medium sized vessels
• ANCA negative
• 30% associated with hepatitis B positivity
• incidence 0.7 per 100,000; affects individuals between 40-60 yr; M:F = 2:1
Table 23. Classification Criteria for PAN*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Weight loss</td>
<td>&gt;4 kg, not due to dieting or other factors</td>
</tr>
<tr>
<td>2. Myalgias, weakness, or leg tenderness</td>
<td>Diffuse myalgias or weakness</td>
</tr>
<tr>
<td>3. Livedo reticularis</td>
<td>Mottled, reticular pattern over skin</td>
</tr>
<tr>
<td>4. Neuropathy</td>
<td>Mononeuropathy, mononeuropathy multiplex, or polyneuropathy</td>
</tr>
<tr>
<td>5. Testicular pain or tenderness</td>
<td>Not due to infection, trauma, or other causes</td>
</tr>
<tr>
<td>6. dBP &gt;90 mmHg</td>
<td>Development of HTN with dBP &gt;90 mmHg</td>
</tr>
<tr>
<td>7. Elevated Cr or BUN</td>
<td>Cr &gt;130 µmol/L (1.5 mg/dL), BUN &gt;14.3 mmol/L (40 mg/dL)</td>
</tr>
<tr>
<td>8. Hepatitis B positive</td>
<td>Presence of hepatitis B surface antigen or Ab</td>
</tr>
<tr>
<td>9. Arteriographic abnormality</td>
<td>Commonly aneurysms</td>
</tr>
<tr>
<td>10. Biopsy of artery</td>
<td>Presence of granulocytes and/or mononuclear leukocytes in the artery wall</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 10 criteria present  
American College of Rheumatology, 1990

**Etiology and Pathophysiology**
- focal panmural necrotizing inflammatory lesions in small and medium-sized arteries
- thrombosis, aneurysm, or dilatation at lesion site may occur
- healed lesions show proliferation of fibrous tissue and endothelial cells that may lead to luminal occlusion

**Investigations**
- blood work: CBC, ESR, Cr, BUN, p-ANCA, hepatitis B serology
- imaging: angiography
- arterial biopsy

**Treatment**
- prednisone 1 mg/kg/d PO and cyclophosphamide 2 mg/kg/d PO
- ± anti-viral therapy to enhance clearance of hepatitis B virus

### Large Vessel Vasculitis
- see Ophthalmology, OP38

**GCA/TEMPORAL ARTERITIS**

Table 24. Classification Criteria for GCA*

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age at onset ≥50</td>
<td>Often temporal</td>
</tr>
<tr>
<td>2. New H/A</td>
<td>Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis</td>
</tr>
<tr>
<td>3. Temporal artery abnormality</td>
<td>Temporal artery tenderness or decreased pulsations, not due to arteriosclerosis</td>
</tr>
<tr>
<td>4. Elevated ESR</td>
<td>ESR ≥50 mm/h</td>
</tr>
<tr>
<td>5. Abnormal artery biopsy</td>
<td>Mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells</td>
</tr>
</tbody>
</table>

*Diagnosed if 3 or more of the above 5 criteria present  
American College of Rheumatology, 1990

**Epidemiology**
- most frequent vasculitis in North America
- patients >50 yr
- F:M = 2:1
- North-South gradient (predominance in Northern Europe/US)
- affects extracranial arteries

**Signs and Symptoms**
- new onset temporal H/A ± scalp tenderness due to inflammation of involved portion of the temporal or occipital arteries
- sudden, painless loss of vision and/or diplopia due to narrowing of the ophthalmic or posterior ciliary arteries (PCA more common); can affect both eyes
- tongue and jaw claudication (pain in muscles of mastication on prolonged chewing)
- PMR (proximal myalgia, constitutional symptoms, elevated ESR) occurs in 30% of patients
- aortic arch syndrome (involvement of subclavian and brachial branches of aorta resulting in pulseless disease), aortic aneurysm ± rupture are late complications

**Medical Emergency**
Untreated, GCA can lead to permanent blindness in 20-25% of patients
Treat on clinical suspicion
Investigations
- diagnosis made by clinical suspicion, increased ESR, increased CRP, temporal artery biopsy within 14 d of starting steroids, possible U/S

Treatment
- if suspect GCA, immediately start high dose prednisone 1 mg/kg in divided doses for approximately 4 wk, and then tapering prednisone as symptoms resolve; highly effective in treatment and in prevention of blindness and other vascular complications
- consider low dose ASA

Prognosis
- increased risk of thoracic aortic aneurysm and aortic dissection
- yearly CXR ± abdominal U/S as screening

Seronegative Rheumatic Disease

Table 25. A Comparison of the Spondyloarthropathies*

<table>
<thead>
<tr>
<th>Feature</th>
<th>AS</th>
<th>PsA</th>
<th>ReA</th>
<th>EA</th>
</tr>
</thead>
<tbody>
<tr>
<td>M:F</td>
<td>3:1</td>
<td>1:1</td>
<td>8:1</td>
<td>1:1</td>
</tr>
<tr>
<td>Age of Onset</td>
<td>20s</td>
<td>35-45</td>
<td>20s</td>
<td>Any</td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>25%</td>
<td>96%</td>
<td>90%</td>
<td>Common</td>
</tr>
<tr>
<td>Distribution</td>
<td>Axial, LE</td>
<td>LE</td>
<td>LE</td>
<td></td>
</tr>
<tr>
<td>Sacroiliitis</td>
<td>100%</td>
<td>40%</td>
<td>80%</td>
<td>20%</td>
</tr>
<tr>
<td>Dactylitis</td>
<td>Uncommon</td>
<td>Common</td>
<td>Occasional</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Enthesitis</td>
<td>Common</td>
<td>Common</td>
<td>Common</td>
<td>Less Common</td>
</tr>
<tr>
<td>Skin Lesions</td>
<td>Rare</td>
<td>100%</td>
<td>Common</td>
<td>Occasional</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Psoriasis eventually 70% at onset of arthritis</td>
<td>Keratoderma</td>
<td>Pyoderma, erythema nodosum</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Common</td>
<td>Occasional</td>
<td>20%</td>
<td>Rare</td>
</tr>
<tr>
<td>Urethritis</td>
<td>Rare</td>
<td>Uncommon</td>
<td>Common</td>
<td>Rare</td>
</tr>
<tr>
<td>HLA-B27</td>
<td>90-95%</td>
<td>40%</td>
<td>80%</td>
<td>30%</td>
</tr>
</tbody>
</table>

LE = lower extremities

*Spondyloarthropathy: inflammatory joint disease of the vertebral column

Ankylosing Spondylitis

Definition
- chronic inflammatory arthritis involving the sacroiliac joints and vertebrae
- enthesitis is a major feature
- prototypical spondyloarthropathy

Table 26. ASAS Classification Criteria for Axial Spondyloarthritis*

<table>
<thead>
<tr>
<th>AS Features</th>
<th>Sacroiliitis on Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>• HLA-B27 positive</td>
<td>• Active (acute) inflammation on MRI highly suggestive of sacroiliitis associated with AS</td>
</tr>
<tr>
<td>• Inflammatory back pain</td>
<td>• Definite radiographic sacroiliitis ≥ grade 2 bilaterally or grade 3-4 unilaterally</td>
</tr>
<tr>
<td>• Arthritis</td>
<td></td>
</tr>
<tr>
<td>• Enthesitis (heel)</td>
<td></td>
</tr>
<tr>
<td>• Uveitis</td>
<td></td>
</tr>
<tr>
<td>• Dactylitis</td>
<td></td>
</tr>
<tr>
<td>• Psoriasis</td>
<td></td>
</tr>
<tr>
<td>• Crohn’s disease/colitis</td>
<td></td>
</tr>
<tr>
<td>• Good response to NSAIDs</td>
<td></td>
</tr>
<tr>
<td>• Family history of AS</td>
<td></td>
</tr>
<tr>
<td>• Elevated CRP</td>
<td></td>
</tr>
</tbody>
</table>

*For patients with ≥3 mc back pain and age at onset <45 yr

Etiology and Pathophysiology
- inflammation → osteopenia → erosion → ossification → osteoproliferation (syndesmophytes)

Rule of 2s
- AS occurs in 0.2% of the general population
- 2% of HLA-B27 positive individuals
- 20% of HLA-B27 positive individuals with affected family member
# Epidemiology
- M:F = 3:1; females have milder disease which may be under-recognized and more peripheral arthritis and upper spine spondylitis.
- 90-95% of patients have HLA-B27 (9% HLA-B27 positive in general population).

## Signs and Symptoms
### Axial
- Mid and lower back stiffness, prolonged morning stiffness, night pain, persistent buttock pain, painful sacroiliac joint (FABER test).
- Spinal restriction (decreased ROM): lumbar (decreased Schöber), thoracic (decreased chest wall expansion).
- Postural changes: decreased lumbar lordosis + increased thoracic kyphosis + increased cervical flexion = increased occiput to wall distance (>5 cm).

### Peripheral
- Asymmetrical large joint arthritis, most often involving lower limb.
- Enthesitis: tenderness over tibial tuberosity or Achilles tendon and plantar fascia insertions into the calcaneus.

### Extra-Articular Manifestations
- Ophthalmic: acute anterior uveitis is common (25-30% patients).
- Renal: amyloidosis (late and rare), IgA nephropathy.
- Gastrointestinal: IBD.
- Cardiac: aortitis, aortic regurgitation, pericarditis, conduction disturbances, heart failure (rare).
- Respiratory: apical fibrosis (rare).
- Neurologic: cauda equina syndrome (rare).
- Skin: psoriasis.

## Investigations
- X-ray of SI joint: "pseudowidening" of joint due to erosion and joint sclerosis → bony fusion (late), symmetric sacroiliitis.
- X-ray of spine: "squaring of edges" from erosion and sclerosis on corners of vertebral bodies (shiny corner sign) leading to ossification of outer fibres of annulus fibrosis (bridging syndesmophytes) → "bamboo spine" radiographically.
- MRI of spine: assess activity in early disease; detection of cartilage changes, bone marrow edema, bone erosions, and subchondral bone changes. Best seen on T2 STIR (short tau inversion recovery) images (suppress fat and see bone edema).

## Treatment
### Non-Pharmacological Therapy
- Prevent fusion from poor posture and disability through exercise (e.g., swimming), postural and deep breathing exercises, outpatient PT, smoking cessation.

### Pharmacological Therapy
- NSAIDs (first line of treatment).
- Glucocorticoids (topical eye drops, local injections).
- DMARDs for peripheral arthritis (sulfasalazine, MTX).
- Biologics for axial and peripheral involvement.
- Manage extra-articular manifestations.

### Surgical Therapy
- Hip replacement, vertebral osteotomy for marked deformity.

## Table 27. Types of Back Pain

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mechanical</th>
<th>Inflammatory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Past History</td>
<td>±</td>
<td>++</td>
</tr>
<tr>
<td>Family History</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Insidious</td>
</tr>
<tr>
<td>Age</td>
<td>15-90 yr</td>
<td>&lt;40 yr</td>
</tr>
<tr>
<td>Sleep Disturbance</td>
<td>±</td>
<td>+ + (worse during 2nd half of night)</td>
</tr>
<tr>
<td>Morning Stiffness</td>
<td>&lt;30 min</td>
<td>&gt;1 h</td>
</tr>
<tr>
<td>Involvement of Other Systems</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Exercise</td>
<td>Worse</td>
<td>Better</td>
</tr>
<tr>
<td>Rest</td>
<td>Better</td>
<td>Worse</td>
</tr>
<tr>
<td>Radiation of Pain</td>
<td>Anatomic (L5-S1)</td>
<td>Diffuse (thoracic, buttock)</td>
</tr>
<tr>
<td>Sensory Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Motor Symptoms</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>
Prognosis
• spontaneous remissions and relapses are common and can occur at any age
• function may be excellent despite spinal deformity
• favourable prognosis if female and age of onset >40 yr
• early onset with hip disease may lead to severe disability; may require arthroplasty

Enteropathic Arthritis
• see Gastroenterology, Inflammatory Bowel Disease, G19
• MSK manifestations in the setting of either ulcerative colitis or Crohn’s disease include peripheral arthritis (large joint, asymmetrical), spondylitis, and hypertrophic osteoarthropathy
• non-arthritic MSK manifestations can occur 2º to steroid treatment of bowel inflammation (arthralgia, myalgia, osteoporosis, AVN)
• NSAIDs should be used cautiously as they may exacerbate bowel disease

Table 28. Comparing Features of Spondylitis vs. Peripheral Arthritis in EA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Spondylitis</th>
<th>Peripheral Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-B27 Association</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Onset Before IBD</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Parallels IBD Course</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Type of IBD Course</td>
<td>UC=CD</td>
<td>CD</td>
</tr>
</tbody>
</table>

Psoriatic Arthritis

Definition
• arthritic inflammation associated with psoriasis

Etiology and Pathophysiology
• unclear but many genetic, immunologic, and some environmental factors involved (e.g. bacterial, viral, and trauma)

Epidemiology
• psoriasis affects 1% of population
• arthropathy in 15% of patients with psoriasis
• 15-20% of patients will develop joint disease before skin lesions appear

Signs and Symptoms
• dermatologic
  • well-demarcated erythematos plaques with silvery scale
  • nail involvement: pitting, transverse or longitudinal ridging, discoloration, subungual hyperkeratosis, onycholysis, and oil drops
• musculoskeletal
  • 5 general patterns
    • asymmetric oligoarthritis (most common – 70%)
    • arthritis of DIP joints with nail changes
    • destructive (mutilans) arthritis (5%)
    • symmetric polyarthritis (similar to RA)
    • sacroiliitis and spondylitis (usually older, male patients)
  • other findings: dactylitis, enthesopathy
• ophthalmic
  • conjunctivitis, iritis (anterior uveitis)
• cardiac and respiratory (late findings)
  • aortic insufficiency
  • apical lung fibrosis
• neurologic
  • cauda equina syndrome
• radiologic
  • floating syndesmophytes
  • pencil-in-cup appearance at IP joints
  • osteolysis, periostitis

Treatment
• treat skin lesions (e.g. steroid cream, salicylic and/or retinoic acid, tar, UV light)
• NSAIDs or IA steroids
• DMARDs, biologic therapies to minimize erosive disease (use early if peripheral joint involvement)

Risks and Benefits of Tumour Necrosis Factor-alpha (TNF-α) Inhibitors in the Management of Psoriatic Arthritis (PsA): Systematic Review and Meta-analysis of Randomized Controlled Trials
J Rheumatol 2008;35:883-890
Study: Review of RCTs of adalimumab, etanercept, and infliximab used in patients with PsA.
Results: Six RCTs were included (n=1820). All 3 TNF-α inhibitors were significantly more effective than placebo on the basis of Psoriatic Arthritis Response Criteria (PsARC) and American College of Rheumatology response criteria ACR20, ACR50, and ACR70 ratings. There were no significant differences between TNF-α inhibitors and placebo in the proportions of patients who withdrew for any reason (RR 0.48, 95% CI 0.20-1.18), or withdrawal due to adverse events (RR 2.14, 95% CI 0.73-6.27), serious adverse events (RR 0.98, 95% CI 0.56-1.77), or upper respiratory tract infections (RR 0.91, 95% CI 0.55-1.52). Pooled rates for injection site reactions were significantly higher for adalimumab and etanercept than for placebo (RR 2.48, 95% CI 1.16-5.29), but there was no significant difference in the proportion of patients experiencing infusion reactions with infliximab (RR 1.03, 95% CI 0.48-2.20) compared to placebo. Indirect analysis did not demonstrate any significant differences between the TNF-α inhibitors.

Conclusions: TNF-α inhibitors are effective treatments for PsA with no important added risks associated with their short-term use. There is still a need for long-term risk-benefit assessment of use of these drugs for the management of PsA.
Table 29. CASPAR Criteria for PsA*

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Evidence of psoriasis</td>
<td>Current, past, or family history</td>
</tr>
<tr>
<td>2. Psoriatic nail dystrophy</td>
<td>Onycholysis, pitting, hyperkeratosis</td>
</tr>
<tr>
<td>3. Negative results for RF</td>
<td>Current or past history</td>
</tr>
<tr>
<td>4. Dactylitis</td>
<td>Juxta articular bone formation on hand or foot x-rays</td>
</tr>
</tbody>
</table>

* To meet the CASPAR (ClASsification criteria for Psoriatic ARthritis) criteria, a patient must have inflammatory articular disease (joint, spine, or enthesitis) with ≥2 points from the above 5 categories.


Reactive Arthritis

Definition

- two meanings
  1. reactive arthritis: a sterile arthritis following an infection (e.g. rheumatic fever, post-viral arthritis, etc.), not used frequently by rheumatologists
  2. reactive arthritis (ReA): one of the seronegative spondyloarthropathies in which patients have a peripheral arthritis (≥1 mo duration) accompanied by one or more extra-articular manifestations that appears shortly after certain infections of the GI or GU tracts

Etiology

- onset following an infectious episode either involving the GI or GU tract
  - GI: Shigella, Salmonella, Campylobacter, Yersinia species
  - GU: Chlamydia (isolated in 16-44% of ReA cases), Mycoplasma species
- acute clinical course
  - 1-4 wk post-infection
  - lasts weeks to years
  - often recurring
  - spinal involvement persists

Epidemiology

- in HLA-B27 patients, axial > peripheral involvement
- M>F

Signs and Symptoms

- musculoskeletal
  - peripheral arthritis, asymmetric pattern, spondylitis, Achilles tendinitis, plantar fasciitis, dactyitis
- ophthalmic
  - iritis (anterior uveitis), conjunctivitis
- dermatologic
  - keratoderma blennorrhagium (hyperkeratotic skin lesions on palms and soles) and balanitis cinerinata (small, shallow, painless ulcers of glans penis and urethral meatus) are diagnostic
- gastrointestinal
  - oral ulcers, diarrhea
- urethritis and cervicitis
  - sterile pyuria; presence not related to site of initiating infection

Investigations

- diagnosis is clinical plus laboratory
- blood work: normocytic, normochromic anemia, and leukocytosis
- sterile cultures
- serology: HLA-B27 positive

Treatment

- antibiotics for non-articular infections
- NSAIDs, physical therapy, exercise
- local therapy
  - joint protection
  - IA steroid injection
  - topical steroid for ocular involvement
- systemic therapy
  - corticosteroids, sulfasalazine, MTX (for peripheral joint involvement only)
  - TNF-α inhibitors for spinal inflammation

Prognosis

- self-limited, typically 3-5 mo, varies based on pathogen and patient’s genetic background
- chronic in 15-20% of cases
Crystal-Induced Arthropathies

### Table 30. Gout vs. Pseudogout

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gout</th>
<th>Pseudogout</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>M&gt;F</td>
<td>M=F</td>
</tr>
<tr>
<td>Age</td>
<td>Middle-aged males</td>
<td>Age &gt; 60 yr</td>
</tr>
<tr>
<td>Onset of Disease</td>
<td>Acute</td>
<td>Acute/insidious</td>
</tr>
<tr>
<td>Crystal Type</td>
<td>Monosodium urate</td>
<td>CPPD</td>
</tr>
<tr>
<td>Distribution</td>
<td>First MTP classically; also midfoot, ankle,knee, or polyarticular</td>
<td>Knee, wrist; monoarticular, or polyarticular if chronic</td>
</tr>
<tr>
<td>Radiology (note findings are non-specific)</td>
<td>Erosions</td>
<td>Chondrocalcinosis</td>
</tr>
<tr>
<td>Treatment</td>
<td>Acute: NSAIDs, corticosteroids, colchicine</td>
<td>NSAIDs, corticosteroids</td>
</tr>
</tbody>
</table>

#### Gout

**Definition**
- derangement in purine metabolism resulting in hyperuricemia; monosodium urate crystal deposits in tissues (tophi) and synovium (microtophi)

**Etiology and Pathogenesis**
- sources of uric acid: diet and endogenous synthesis
  - hypoxanthine $\rightarrow$ xanthine $\rightarrow$ uric acid
  - both steps catalyzed by xanthine oxidase

**Hyperuricemia**
- primary or genetic
  - mostly due to idiopathic renal underexcretion (90%)
  - also idiopathic overproduction or abnormal enzyme production/function
- secondary
  - dietary excess (particularly high consumption of beer, seafood, and meat)
  - underexcretion (<90%): renal failure, drugs, systemic conditions
  - overproduction (<10%): increased nucleic acid turnover states (e.g. malignancy, post-chemotherapy)

- sudden changes (increasing or decreasing) in uric acid concentration are more important than absolute values
  - acute gout can occur with normal serum uric acid
  - changes in pH, temperature, or initiation of antihyperuricemics may precipitate an acute gouty attack
- common precipitants: alcohol, dietary excess, dehydration, drugs (e.g. thiazide and loop diuretics), trauma, illness, surgery, starting xanthine oxidase inhibitor therapy
- other associated conditions: HTN, obesity, DM, starvation

**Epidemiology**
- most common in males >45 yr
- extremely rare in premenopausal females

**Signs and Symptoms**
- single episode progressing to recurrent episodes of acute inflammatory arthritis
- acute gouty arthritis
  - severe pain, redness, joint swelling, usually involving lower extremities
  - joint mobility may be limited
  - attack will subside spontaneously within several days to weeks; may recur
- tophi
  - urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
  - common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- kidney
  - gouty nephropathy
  - uric acid calculi

**Investigations**
- joint aspirate: >90% of joint aspirates show crystals of monosodium urate (negatively birefringent, needle-shaped)
- x-rays may show tophi as soft tissue swelling, punched-out lesions, erosion with “over-hanging”
- X-rays may show tophi as soft tissue swelling, punched-out lesions, erosion with “over-hanging”
- urate deposits on cartilage, tendons, bursae, soft tissues, and synovial membranes
- common sites: first MTP, ear helix, olecranon bursae, tendon insertions (common in Achilles tendon)
- kidney
- gouty nephropathy
- uric acid calculi

- Normal or low uric acid levels do not rule out gout

- The majority of people with hyperuricemia do not have gout
- An acute gout attack may mimic cellulitis; however, joint mobility is preserved in cellulitis
- Gout often affects more than one joint (i.e. ankle, midfoot, and MTPs)

- Allopurinol can be used in patients with mild/moderate disease
- NSAIDs, corticosteroids, colchicine
- X-rays may show tophi as soft tissue swelling, punched-out lesions, erosion with “over-hanging”
**Treatment**

- **acute gout**
  - NSAIDs: high dose, then taper as symptoms improve
  - corticosteroids: IA, oral, or intra-muscular (if renal, cardiovascular, or GI disease and/or if NSAIDs contraindicated or failed)
  - colchicine within first 12 h but effectiveness limited by narrow therapeutic range
  - allopurinol can worsen an acute attack (do not start during acute flare)

- **chronic gout**
  - conservative
    - avoid foods with high purine content (e.g. visceral meats, sardines, shellfish, beans, peas)
    - avoid drugs with hyperuricemic effects (e.g. pyrazinamide, ethambutol, thiazide, alcohol)
  - medical
    - antihyperuricemic drugs (allopurinol and febuxostat): decrease uric acid production by inhibiting xanthine oxidase
    - uricosuric drugs (probenecid, sulfinpyrazone): use if failure on or intolerant to allopurinol; do not use in renal failure
    - prophylaxis prior to starting antihyperuricemic drugs (colchicine/low-dose NSAID)
    - in renal disease secondary to hyperuricemia, use low-dose allopurinol and monitor Cr

- indications for treatment with antihyperuricemic medications include
  - recurrent attacks, tophi, bone erosions, urate kidney stones
  - perhaps in renal dysfunction with very high urate load (controversial)

---

**Pseudogout (Calcium Pyrophosphate Dihydrate Disease)**

**Definition**
- joint inflammation caused by calcium pyrophosphate crystals

**Etiology and Pathophysiology**
- acute inflammatory arthritis due to phagocytosis of IgG-coated CPPD crystals by neutrophils and subsequent release of inflammatory mediators within joint space
- more frequently polyarticular
- slower in onset in comparison to gout, lasts up to 3 wk but is self-limited

**Risk Factors**
- old age, advanced OA, neuropathic joints
- other associated conditions: hyperparathyroidism, hypothyroidism, hypomagnesemia, hypophosphatasia (low ALP), DM, hemochromatosis

**Signs and Symptoms**
- affects knees, wrists, MCPs, hips, shoulders, elbows, ankles, big toe
- multiple manifestations
  - asymptomatic crystal deposition (seen on radiograph only)
  - acute crystal arthritis (self-limited flares of acute inflammatory arthritis resembling gout)
  - pseudo-OA (progressive joint degeneration, sometimes with episodes of acute inflammatory arthritis)
  - pseudo-RA (symmetrical polyarticular pattern with morning stiffness and constitutional symptoms)
- acute may be triggered by dehydration, acute illness, surgery, trauma

**Investigations**
- must aspirate joint to rule out septic arthritis, gout
- CPPD crystals: present in 60% of patients, often only a few crystals, positive birefringence (blue) and rhomboid shaped
- x-rays show chondrocalcinosis in 75%: radiodensities in fibrocartilaginous structures (e.g. knee menisci) or linear radiodensities in hyaline articular cartilage

**Treatment**
- joint aspiration, rest, and protection
- NSAIDs: also used for maintenance therapy
- prophylactic colchicine PO (controversial)
- IA or oral steroids to relieve inflammation
Non-Articular Rheumatism

Definition
• disorders that primarily affect soft tissues or periarticular structures
  • includes bursitis, tendinitis, tenosynovitis, fibromyalgia, and PMR

Polymyalgia Rheumatica

Definition
• characterized by pain and stiffness of the proximal extremities (girdle area)
• closely related to GCA (15% of patients with PMR develop GCA)
• no muscle weakness

Table 31. PMR Classification Criteria Scoring Algorithm*

<table>
<thead>
<tr>
<th>Points without U/S Points with Abnormal U/S**</th>
</tr>
</thead>
<tbody>
<tr>
<td>(0-6)</td>
</tr>
<tr>
<td>Morning stiffness duration &gt;45 min 2 2</td>
</tr>
<tr>
<td>Hip pain or limited ROM 1 1</td>
</tr>
<tr>
<td>Absence of RF or ACPA 2 2</td>
</tr>
<tr>
<td>Absence of other joint involvement 1 1</td>
</tr>
<tr>
<td>At least one shoulder with subdeltoid and/or biceps tenosynovitis and/or glenohumeral synovitis (either posterior or axillary) and at least one hip with synovitis and/or trochanteric bursitis on U/S N/A 1</td>
</tr>
<tr>
<td>Both shoulders with subdeltoid bursitis, biceps tenosynovitis, or gleno-humeral synovitis on U/S N/A 1</td>
</tr>
</tbody>
</table>

*Required criteria: age >50 yr, bilateral shoulder aching, and abnormal ESR/CRP
* A score of 4 or more is categorized as PMR in the algorithm without U/S and a score of 5 or more is categorized as PMR in the algorithm with U/S
**Optional U/S criteria
Ann Rheum Dis 2012;71:484-492

Epidemiology
• incidence 50 per 100,000 per year in those >50 yr
• age of onset typically >50 yr, F:M = 2:1

Signs and Symptoms
• constitutional symptoms prominent (fever, weight loss, malaise)
• pain and stiffness of symmetrical proximal muscles (neck, shoulder and hip girdles, thighs)
• gel phenomenon (stiffness after prolonged inactivity)
• physical exam reveals tender muscles, but no weakness or atrophy

Investigations
• blood work: often shows anemia, elevated platelets, elevated ESR and CRP, and normal CK; up to 5% of PMR reported with normal inflammatory markers

Treatment
• goal of therapy: symptom relief
• start with prednisone dose of 15-20 mg PO OD, reconsider diagnosis if no response within several days
• taper slowly over 2 yr period monitoring ESR and symptoms closely
• relapses should be diagnosed and treated on clinical basis; do not treat a rise in ESR as a relapse
• treat relapses aggressively (50% relapse rate)
• monitor for steroid side effects, glucocorticoid-induced osteoporosis prevention, and follow for symptoms of GCA

Most patients are treated for up to 2 yr
**Fibromyalgia**

**Definition**
- chronic (>3 mo), widespread (axial, left- and right-sided, upper and lower segment), non-articular pain with characteristic tender points

**Diagnosis**

**Table 32. 2010 ACR Preliminary Diagnostic Criteria for Fibromyalgia**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Widespread Pain Index = number of areas in which the patient had pain over the last week (max score = 19):</td>
<td>A patient satisfies diagnostic criteria for fibromyalgia if the following 3 conditions are met:</td>
</tr>
<tr>
<td>L and R: shoulder girdle, upper arm, lower arm, hip, upper leg, lower leg, jaw</td>
<td>1. Widespread Pain Index (WPI) ≥7 and Symptom Severity (SS) scale score ≥5 or WPI 3–6 and SS scale score ≥9</td>
</tr>
<tr>
<td>One Area: chest, abdomen, upper back, lower back, neck</td>
<td>2. Symptoms have been present at a similar level for at least 3 mo</td>
</tr>
<tr>
<td>Symptom Severity Score = sum of:</td>
<td>3. The patient does not have a disorder that would otherwise explain the pain</td>
</tr>
<tr>
<td>a) severity of fatigue</td>
<td></td>
</tr>
<tr>
<td>b) waking unrefreshed</td>
<td></td>
</tr>
<tr>
<td>c) cognitive symptoms over the past week</td>
<td></td>
</tr>
<tr>
<td>d) extent of somatic symptoms (IBS, H/A, abdominal pain/cramps, dry mouth, fever, hives, ringing in ears, vomiting, heartburn, dry eyes, SOB, loss of appetite, rash, hair loss, easy bruising, etc.)</td>
<td></td>
</tr>
<tr>
<td>all (a-d) rated on 0-3 scale: 0 = no problem, 1 = mild, 2 = moderate, 3 = severe</td>
<td></td>
</tr>
</tbody>
</table>

*Arthritis Care and Research 2010;62(s5):S60-S610*

**Epidemiology**
- F:M = 3:1
- primarily ages 25-45 yr, some adolescents
- prevalence of 2-5% in general population
- overlaps with chronic fatigue syndrome and myofascial pain syndrome
- strong association with psychiatric illness

**Signs and Symptoms**
- widespread aching, stiffness
- easy fatigability
- sleep disturbance: non-restorative sleep, difficulty falling asleep, and frequent waking
- symptoms aggravated by physical activity, poor sleep, emotional stress
- patient feels that joints are diffusely swollen although joint examination is normal
- neurologic symptoms of hyperalgesia, paresthesias
- associated with irritable bowel or bladder syndrome, migraines, tension H/A, restless leg syndrome, obesity, depression, and anxiety
- physical exam should reveal only tenderness with palpation of soft tissues, with no specificity for trigger/tender points

**Investigations**
- blood work: includes TSH and ESR; all typically normal unless unrelated, underlying illness present
- serology: do not order ANA or RF unless there is clinical suspicion for a connective tissue disease
- laboratory sleep assessment

**Differential Diagnosis**
- diagnosis of exclusion
- rule out other disorders by history and physical exam (RA, SLE, PMR, myositis, hypothyroidism, hyperparathyroidism, neuropathies)

**Treatment**
- non-pharmacological therapy
  - education
  - exercise program (walking, aquatic exercises), physical therapy (good posture, stretching, muscle strengthening, massage)
  - stress reduction, CBT
  - no evidence for alternative medicine such as biofeedback, meditation, acupuncture

**A 14 Week, RCT of Pregabalin in Patients with Fibromyalgia**

**Study:** Multicentre RCT. 750 patients with fibromyalgia with pain score of <40 mm on the visual analog scale (VAS) were assigned to placebo or pregabalin (300 mg, 450 mg, or 600 mg) daily for 12 wk.

**Primary Outcome:** Change in the mean pain score derived from the subject’s daily pain diary as measured at the patient’s baseline to the end point of the study.

**Results:** Patients treated with 300, 450 and 600 mg/d pregabalin showed a statistically significant improvement in the end point mean pain score compared with placebo-treated subjects. Discontinuations due to adverse events were 12%, 16%, 22%, and 26% in placebo, 300 mg/d, 450 mg/d, and 600 mg/d respectively. The 450 and 600 mg/d groups were significantly different from placebo (p=0.0001).

**Conclusions:** Pregabalin at 300 mg/d, 450 mg/d, and 600 mg/d showed statistically significant response rates as compared to placebo although discontinuation rates for the 450 mg/d and 600 mg/d regimens were significantly higher as compared to placebo.

**Exercise for Treating Fibromyalgia Syndrome**

**Study:** Systematic review of exercise training including cardiorespiratory endurance, muscle strengthening, and flexibility for global well-being and physical function in patients with fibromyalgia.

**Result:** 34 studies were included (n=2,276).

**Conclusion:** Moderate aerobic cardiorespiratory exercise improves function and well-being in patients with fibromyalgia. Benefits from muscle strengthening and flexibility require additional research to delineate benefits.
• pharmacological therapy
  • low dose tricyclic antidepressant (e.g. amitriptyline)
  • for sleep restoration
  • select those with lower anticholinergic side effects
  • SNRI: duloxetine, milnacipran
  • anticonvulsant: pregabalin, gabapentin
  • analgesics may be beneficial for pain that interferes with sleep (NSAIDs, not narcotics)

Prognosis
• variable; usually chronic, unless diagnosed and treated early

### Adult Onset Still’s Disease

#### Definition
• systemic inflammatory condition (ANA and RF negative) with fevers and characteristic rash, numerous systemic symptoms, and may have severe arthritis

#### Etiology and Pathophysiology
• idiopathic; infectious triggers likely – various viruses and bacteria have been implicated
• stress increases risk

#### Epidemiology
• F>M; age of onset typically 16-40, approximately 1 per 100,000

#### Signs and Symptoms
• classic triad of symptoms
  • high-spiking fevers (95.7% of patients, typically T = 39°C, <4 h duration, quotidian pattern)
  • characteristic “salmon rash” (~72% of patients, on proximal limbs + trunk)
  • arthralgia/arthritis (64-100%)
    • arthritis is symmetric, typically affects large joints, i.e. wrists, knees and ankles, may involve PIP and DIPs, elbow, MTPs
  • sore throat, myalgias and serositis may also occur
  • liver abnormalities ± hepatomegaly (50-75% patients)
  • splenomegaly (44%)

#### Classification
• numerous classification systems proposed

<table>
<thead>
<tr>
<th>Table 33. Yamaguchi’s Criteria for Classification of Adult Still’s Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Criteria</strong></td>
</tr>
<tr>
<td>T &gt;39°C, intermittent, &gt;1 wk</td>
</tr>
<tr>
<td>Arthralgias/arthritis ≥2 wks</td>
</tr>
<tr>
<td>Typical rash</td>
</tr>
<tr>
<td>WBC &gt;10,000 (&gt;80% granulocytes)</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

Need 5 criteria for diagnosis, at least 2 major. Exclusion criteria: infection, malignancy, rheumatic disease

#### Investigations
• ANA and RF negative
• markedly elevated ESR, CRP, ferritin (typically >1000 ng/mL)
  • total ferritin >5x ULN = 80% sensitive, 41% specific
  • anemia, thrombocytosis, leukocytosis may occur
  • transaminases, LDH may be elevated

#### Treatment
• biologics (anti-IL-1 and anti-IL-6 agents)
• begin management with low-dose glucocorticoids ± MTX
# Common Medications

## Table 34. Common Medications for Osteoarthritis

<table>
<thead>
<tr>
<th>Class</th>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing (PO)</th>
<th>Indications</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analgesic</td>
<td>acetaminophen</td>
<td>Tylenol®</td>
<td>500 mg tid q4h (4 g daily max)</td>
<td>1st line</td>
<td></td>
<td>Hepatotoxicity, Overdose, Potentiates warfarin</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>ECASA</td>
<td></td>
<td>325-975 mg qid 200-600 mg tid 25-50 mg tid 50-75/200 mg tid 125-500 mg bid 7.5-15 mg OD</td>
<td>2nd line</td>
<td>GI bleed Renal impairment Allergy to ASA, NSAIDs Pregnancy (T3)</td>
<td>Nausea, tinnitus, vertigo, rash, dyspepsia, GI bleed, PUD, hepatitis, renal failure, HTN, nephrotic syndrome</td>
</tr>
<tr>
<td>COX-2 INHIBITORS</td>
<td>celecoxib</td>
<td>Celebrex®</td>
<td>200 mg OD</td>
<td>High risk for GI bleed: age &gt;65 Hx of GI bleed, PUD</td>
<td>Renal impairment Sulf allergy (celecoxib) Cardiovascular disease</td>
<td>Delayed ulcer healing Renal/hepatic impairment Rash</td>
</tr>
</tbody>
</table>

### Other Treatments

- Combination analgesics (acetaminophen + codeine, acetaminophen + NSAIDs)
  - Enhanced short-term effect compared to acetaminophen alone
  - More adverse effects: sedation, constipation, nausea, GI upset
- IA corticosteroid injection
  - Short-term (weeks-months) decrease in pain and improvement in function
  - Used for management of an IA inflammatory process when infection has been ruled out
- IA hyaluronic acid q6mo
  - For mild-moderate OA of the knees, however, little supporting evidence, and not considered to be effective
  - Precaution with chicken/egg allergy
- Topical NSAIDs
  - 25% wt/wt topical diclofenac (Pennsaid®)
    - May use for patients who fail acetaminophen treatment and who wish to avoid systemic therapy
- Capsaicin cream
  - Limited clinical studies
  - No regulation by Health Canada
- Glucosamine sulfate ± chondroitin
  - Limited clinical studies
  - No regulation by Health Canada

## Table 35. Disease Modifying Anti-Rheumatic Drugs (DMARDs)

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing (PO)</th>
<th>Contraindications</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydroxychloroquine</td>
<td>Plaquenil®</td>
<td>400 mg PO OD initially 200-400 mg PO OD maintenance (8.5 mg/kg ideal body weight per day)</td>
<td>Retinal disease, G6PD deficiency</td>
<td>GI symptoms, skin rash, macular damage, neuromyopathy Requires regular ophthalmological screening to monitor for retinopathy</td>
</tr>
<tr>
<td>sulfasalazine</td>
<td>Salazopyrin® Azulfidine® (US)</td>
<td>1000 mg PO bid-tid</td>
<td>Sulf/ASA allergy, kidney disease, G6PD deficiency</td>
<td>GI symptoms, rash, H/A, leukopenia</td>
</tr>
<tr>
<td>methotrexate</td>
<td>Rheumatrex® Folex/Mexate®</td>
<td>7.5-25 mg PO/IM/SC qweekly</td>
<td>Bone marrow suppression, liver disease, significant lung disease, immunodeficiency, pregnancy, EiDH abuse</td>
<td>Oral ulcers, GI symptoms, cirrhosis, myelosuppression, pneumonitis, tubular necrosis</td>
</tr>
<tr>
<td>leflunomide</td>
<td>Arava®</td>
<td>10-20 mg PO OD</td>
<td>Liver disease</td>
<td>Alopoeica, GI symptoms, liver dysfunction, pulmonary infiltrates</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td></td>
<td>2.5-3 mg/kg/d divided and given in 2 doses</td>
<td>Kidney/liver disease, infection, HTN</td>
<td>HTN, decreased renal function, hair growth, tremors, bleeding</td>
</tr>
<tr>
<td>gold (injectable)</td>
<td>Solganal® Myocrysine®</td>
<td>50 mg IM q1wk after gradual introduction</td>
<td>IBD, kidney/liver disease</td>
<td>Rash, mouth soreness/ulcers, proteinuria, marrow suppression</td>
</tr>
<tr>
<td>azathioprine</td>
<td>Imuran®</td>
<td>2/5 mg/kg/d PO once daily</td>
<td>Kidney/liver disease, TPMT deficiency</td>
<td>Rash, pancytopenia (especially ↓ WBC, ↑ AST, ALT), biliary stasis, vomiting, diarrhea</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td></td>
<td>1 g/m²/mo IV as per protocol</td>
<td>Kidney/liver disease</td>
<td>Cardiotoxicity, GI symptoms, hemorrhagic cystitis, nephrotoxicity, bone marrow suppression, sterility</td>
</tr>
</tbody>
</table>
Table 35. Disease Modifying Anti-Rheumatic Drugs (DMARDs) (continued)

<table>
<thead>
<tr>
<th>Generic Drug Name</th>
<th>Trade Name</th>
<th>Dosing</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>etanercept</td>
<td>Enbrel®</td>
<td>25 mg biweekly or 50 mg weekly SC</td>
<td>Fusion protein of TNF receptor and Fc portion of IgG</td>
</tr>
<tr>
<td>infliximab</td>
<td>Remicade®</td>
<td>3-5 mg/kg IV q8wk</td>
<td>Chimeric mouse/human monoclonal anti-TNF</td>
</tr>
<tr>
<td>adalimumab</td>
<td>Humira®</td>
<td>40 mg SC q2wk</td>
<td>Monoclonal anti-TNF</td>
</tr>
<tr>
<td>abatacept</td>
<td>Orencia®</td>
<td>IV infusion</td>
<td>Costimulation modulator of T-cell activation</td>
</tr>
<tr>
<td>rituximab</td>
<td>Rituxan®</td>
<td>2 IV infusions, 2 wk apart</td>
<td>Causes B-cell depletion, binds to CD20</td>
</tr>
<tr>
<td>certolizumab</td>
<td>Cimzia®</td>
<td>400 mg SC q2wk x3 then 200 mg SC q4wk</td>
<td>PEGylated monoclonal anti-TNF</td>
</tr>
<tr>
<td>golimumab</td>
<td>Simponi®</td>
<td>50 mg SC q mo</td>
<td>Monoclonal anti-TNF</td>
</tr>
<tr>
<td>tocilizumab</td>
<td>Actemra®</td>
<td>4-8 mg/kg IV q4wk</td>
<td>Interleukin-6 receptor antagonist</td>
</tr>
</tbody>
</table>

**Landmark Rheumatology Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RHEUMATOID ARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATTEST</td>
<td>Ann Rheum Dis 2008; 67:1096-103</td>
<td>Abatacept and infliximab have similar efficacy in RA patients who have failed MTX</td>
</tr>
<tr>
<td>ATTRACT</td>
<td>Lancet 1999; 354:1932-9</td>
<td>Infliximab and MTX combined are more effective than MTX alone for patients with active RA</td>
</tr>
<tr>
<td>CIMESTRA</td>
<td>Arthritis Rheum 2006; 54:1401-9</td>
<td>Combination of MTX and sulfasalazine is superior to either alone</td>
</tr>
<tr>
<td>COMET</td>
<td>Lancet 2008; 372:375-82</td>
<td>Etanercept add-on therapy increases rates of remission in early RA</td>
</tr>
<tr>
<td>ERA</td>
<td>NEJM 2000; 343:1586-93</td>
<td>Etanercept more rapidly decreases symptoms in early RA compared to MTX</td>
</tr>
<tr>
<td>European Leflunomide Study Group</td>
<td>Lancet 1999; 353:259-66</td>
<td>Leflunomide is equal in efficacy to sulphasalazine</td>
</tr>
<tr>
<td>FIN-RACo</td>
<td>Lancet 1999; 353:1568-73</td>
<td>Combination therapy with DMARDs improves remission rates in early RA</td>
</tr>
<tr>
<td>Infliximab and MTX</td>
<td>NEJM 2000; 343:1594-602</td>
<td>Infliximab combined with MTX reduces joint damage in RA</td>
</tr>
<tr>
<td>Leflunomide Rheumatoid Arthritis Investigators Group</td>
<td>Arch Intern Med 1999; 159:2542-50</td>
<td>Leflunomide is equivalent to MTX therapy and superior to placebo</td>
</tr>
<tr>
<td>PREMIER</td>
<td>Arthritis Rheum 2006; 54:26-37</td>
<td>Combination therapy with adalimumab and MTX is superior to either alone in patients with early RA</td>
</tr>
<tr>
<td>Swefot</td>
<td>Lancet 2009; 374:459-66</td>
<td>Anti-TNF agents are more effective second-line therapy than DMARDs in patients who fail MTX</td>
</tr>
<tr>
<td><strong>OSTEOARTHRITIS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAIT</td>
<td>NEJM 2006; 354:795-808</td>
<td>Glucosamine, chondroitin, and the combination of both are no more effective than placebo in treatment of knee OA</td>
</tr>
<tr>
<td><strong>SLE</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belimumab</td>
<td>Lancet 2011; 377:721-31</td>
<td>Treatment with belimumab reduces the incidence of BILAG A and B flares in patients with SLE compared to placebo</td>
</tr>
<tr>
<td>BILAG open-RCT</td>
<td>Rheumatology 2010; 49:723-32</td>
<td>Low dose cyclosporine and azathioprine are equivalent in efficacy as maintenance therapy for SLE</td>
</tr>
<tr>
<td>Mycophenylate mofetil or intravenous cyclophosphamide</td>
<td>NEJM 2005; 353:2219-28</td>
<td>Mycophenylate mofetil is more efficacious than cyclophosphamide in inducing remission of SLE nephritis</td>
</tr>
<tr>
<td><strong>CONNECTIVE TISSUE DISEASES</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azathioprine or MTX maintenance for ANCA-associated vasculitis</td>
<td>NEJM 2008; 359:2790-803</td>
<td>MTX and azathioprine are equally safe and effective as maintenance agents in ANCA vasculitis</td>
</tr>
</tbody>
</table>

**Risks of Biologics**
- Reactivation of TB or hepatitis B. Patients require negative TB skin test, chest x-ray and negative hepatitis B virus serology prior to starting any of these medications
- Increased risk of serious infections
- Worsening heart failure

**CONNECTIVE TISSUE DISEASES**

- Azathioprine or MTX maintenance for ANCA-associated vasculitis
<table>
<thead>
<tr>
<th>Trial</th>
<th>Reference</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide in scleroderma lung disease</td>
<td>NEJM 2006; 354:2655-66</td>
<td>Cyclophosphamide therapy leads to transient improvements in lung function, skin scores, and overall health in patients with scleroderma</td>
</tr>
<tr>
<td>Etanercept plus standard therapy for granulomatosis with polyangiitis</td>
<td>NEJM 2005; 352:351-61</td>
<td>Etanercept is not effective in inducing remission in patients with ANCA vasculitis</td>
</tr>
<tr>
<td>Mycophenolate mofetil vs. azathioprine for maintenance in ANCA-associated vasculitis</td>
<td>JAMA 2010; 304:2381-8</td>
<td>Mycophenolate mofetil is less effective than azathioprine for maintaining disease in ANCA-associated vasculitis</td>
</tr>
<tr>
<td>Rituximab versus cyclophosphamide for ANCA-associated vasculitis</td>
<td>NEJM 2010; 363:221-32</td>
<td>Rituximab is not inferior to cyclophosphamide for induction of remission in ANCA vasculitis</td>
</tr>
</tbody>
</table>

**GOUT**

| Febuxostat vs. allopurinol | NEJM 2005; 353:2450-61 | Febuxostat is more effective than allopurinol at lowering serum urate, and has similar effectiveness on flare reduction |

**ANKYLOSING SPONDYLITIS**

| Adalimumab | Arthritis Rheum 2006; 54:2136-46 | Adalimumab induced partial remission in 22% of AS patients |
| ASSET (rituximab) | Arthritis Rheum 2005; 52:582-91 | Sixty percent of patients treated with rituximab had a clinical response to the medication |
| ATLAS (adalimumab) | J Rheumatol 2008; 35:1346-53 | Compared to placebo, adalimumab significantly reduces pain and fatigue in AS patients |
| Infliximab in AS | Lancet 2005; 36:1187-93 | Infliximab induces regression of symptoms in 50% of patients and is superior to placebo |
| SPINE (etanercept) | Ann Rheum Dis 2011; 70:799-804 | Etanercept has short-term efficacy for patients with advanced AS and reduces disease severity |
| Salsalazine | Arthritis Rheum 1995; 38:618-27 | Salsalazine is superior to placebo in treatment of patients with seronegative spondyloarthropathy |

**References**


Reid G, Enckle JM. Getting the most out of radiology. CMAJ 2000;162:1318-1325.


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• recall that the anatomical position of the penis is erect; therefore, the anatomical ventral side of the penis appears to be the dorsal side of the flaccid penis.
Urologic History

- follow the OPQRSTUW approach
  - note that pain may not be limited to the genital region (e.g. lower abdomen, CVA)
- inquire about risk factors: past urologic disease (e.g. UTI, stones, STI, cancers, anatomic abnormalities, family Hx, medications, lifestyle factors, trauma, previous surgical procedures)
- urinary habits
  - frequency of voiding, quality of urine, volume of voids, incontinence, nocturia
  - specific urinary symptoms include
    - storage symptoms: frequency, nocturia, urgency
    - voiding symptoms: straining, hesitancy, dysuria, intermittency, post-void dribbling, reduced stream, feeling of incomplete voiding
    - hematuria: part of stream during which bleeding occurs, blood clots
    - incontinence: rushing to washroom (urge); leakage with coughing, sneezing, laughing (stress); constant dribbling (overflow)
- sexual function
  - scrotal mass: see Scrotal Mass, U29
  - ED: see Erectile Dysfunction, U30
  - infertility: see Infertility, U34
- risk factors
  - past urologic disease (e.g. UTI, stones, cancers, STI), anatomic abnormalities, trauma, previous surgical procedures, medications, family Hx, lifestyle factors
- associated symptoms
  - N/V
  - bowel dysfunction
- constitutional symptoms
  - fever, chills, unintentional weight loss, night sweats, fatigue, malaise

Always ask about sexual function on history. Change in erectile function can be one of the first symptoms that there is concomitant vascular disease. If there is new onset ED, consider screening for DM and CAD risk factors.
Hematuria (Blood in the Urine)

Macroscopic (Gross) Hematuria

Definition
• blood in the urine that can be seen with the naked eye

Classification
• see Nephrology, NP20

Etiology

Table 1. Etiology by Age Group

<table>
<thead>
<tr>
<th>Age (yr)</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-20</td>
<td>UTI, glomerulonephritis, congenital abnormalities</td>
</tr>
<tr>
<td>20-40</td>
<td>UTI, stones, bladder tumor</td>
</tr>
<tr>
<td>40-60</td>
<td>Male: bladder tumour, stones, UTI</td>
</tr>
<tr>
<td></td>
<td>Female: UTI, stones, bladder tumour</td>
</tr>
<tr>
<td>&gt;60</td>
<td>Male: BPH, bladder tumour, UTI, RCC</td>
</tr>
<tr>
<td></td>
<td>Female: bladder tumour, UTI, RCC</td>
</tr>
</tbody>
</table>

Table 2. Etiology by Type

<table>
<thead>
<tr>
<th>Pseudohematuria</th>
<th>Infectious/Inflammatory</th>
<th>Malignancy</th>
<th>Benign</th>
<th>Structural</th>
<th>Hematologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal bleeding</td>
<td>Vaginosis, Cystitis</td>
<td>RCC (mainly in adult population)</td>
<td>BPH</td>
<td>Stones</td>
<td>Antiocoagulants</td>
</tr>
<tr>
<td>Dyes (beets, rhodamine B in candy and juices)</td>
<td>Urethritis, Glomerulonephritis, Interstitial nephritis, Tuberculosis</td>
<td>UCC, Wilms’ tumour (mainly in pediatric population)</td>
<td>Polycystic kidneys</td>
<td>Coagulation defects</td>
<td></td>
</tr>
<tr>
<td>Hemoglobin (hemolytic anemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myoglobin (rhabdomyolysis)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drugs (rifampin, phenazopyridine, phenytoin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Porphyria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxatives (phenolphthalein)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

History
• inquire about timing of hematuria in urinary stream
  • initial: anterior urethra
  • terminal: bladder neck and prostatic urethra
  • total: bladder and/or above

Investigations
• CBC (rule out anemia, leukocytosis), electrolytes, Cr, BUN, INR, PTT
• urine studies
  • U/A, C&S, cytology
• imaging
  • CT (with contrast) has largely replaced IVP to investigate upper tracts
    • consider contraindications to contrast: allergy, renal insufficiency
    • U/S alone is not sufficient
  • cystoscopy to investigate lower tract (possible retrograde pyelogram)

Acute Management of Severe Bladder Hemorrhage
• manual irrigation via catheter with normal saline to remove clots
• CBI using large (22-26 Fr) 3-way Foley to help prevent clot formation
• cystoscopy if active bleeding
  • identify resectable tumours
  • coagulate obvious sites of bleeding
• refractory bleeding
  • intravesical agents
    • continuous intravesical irrigation with 1% aluminum potassium sulfate solution as needed
    • intravesical instillation of 1% silver nitrate solution
    • intravesical instillation of 1-4% formalin (requires GA and pre-procedure cystogram to rule out reflux)
• embolization or ligation of iliac arteries
• cystectomy and diversion (rarely performed)

Common Urologic Causes of Hematuria can be Classified as:
TICS
• Trauma/Tumour/Toxins
• Infection/Inflammatory
• Calculi/Cysts
• Surgery/Sickle cell and other hematological causes

Upper Tract Imaging Options
CT Urography (CTU): Optimal test for renal parenchyma, calculi, and infections. Involves exposure to radiation and IV contrast. Assess kidney function, allergies prior to use of contrast
U/S: Superior to IVP for evaluation of renal parenchyma and renal cysts. Limited sensitivity for UCC and small renal masses. U/S alone is not sufficient for upper tract imaging
Intravenous Pyelogram (IVP): Traditional option but rarely used (replaced by CTU). Reasonable sensitivity for UCC, but poor sensitivity for RCC
Microscopic Hematuria

Definition
- blood in the urine that is not visible to the naked eye
- >3 RBCs/HPF on urinalysis of at least two separate samples

Figure 6. Workup of asymptomatic microscopic hematuria
Based on CUA Guidelines. Alternatively, the AUA recommends cystoscopy and CT urogram for all patients with confirmed microscopic hematuria; follow-up for negative workup is urinalysis yearly for two years, with repeat anatomic evaluation if microscopic hematuria persists

Lower Urinary Tract Dysfunction

- see Gynecology, GY37 for relevant female topics

Voiding

- two phases of lower urinary tract function
  1. storage phase (bladder filling and urine storage)
     • accommodation and compliance
     • no involuntary contraction
  2. voiding phase (bladder emptying)
     • coordinated detrusor contraction
     • synchronous relaxation of outlet sphincters
     • no anatomic obstruction
- voiding dysfunction can therefore be classified as
  • failure to store: due to bladder or outlet
  • failure to void: due to bladder or outlet
- three types of symptoms
  • storage (formerly known as irritative)
  • voiding (formerly known as obstructive)
  • post-voiding

Urinary Incontinence

Definition
- involuntary leakage of urine

Etiology
- urgency incontinence
  • detrusor overactivity
    • CNS lesion, inflammation/infection (cystitis, stone, tumour), bladder neck obstruction (tumour, stone), BPH, idiopathic

Lower Urinary Tract Symptoms (LUTS)
- Storage (FUND)
  - Frequency
  - Urgency
  - Nocturia
- Dysuria
- Voiding (SHED)
  - Stream changes
  - Hesitancy
  - Incomplete Emptying
  - Dribbling
decreased compliance of bladder wall (inability to store urine)
- CNS lesion, fibrosis
- sphincter/urethral problem
- stress urinary incontinence (SUI)
- common in women; seen in men after prostate cancer treatment or pelvic operations
- urethral hypermobility
- weakened pelvic floor and musculofascial urethral and vaginal supporting mechanisms allows bladder neck and urethra to descend with increased intra-abdominal pressure
- urethra is pulled open by greater motion of posterior wall of outlet relative to anterior wall
- associated with childbirth, pelvic surgery, aging, levator muscle weakness, obesity
- intrinsic sphincter deficiency (ISD): weakness of the urethra and associated smooth and striated muscle elements
- pelvic surgery, neurologic problem, aging and hypoestrogen state
- ISD and urethral hypermobility can co-exist
- mixed incontinence
- combination of stress and urgency incontinence
- overflow incontinence
- is a term sometimes used to describe urinary incontinence as a complication of urinary retention; for causes of urinary retention see Table 4
- use of the term should be accompanied by the associated pathophysiology (e.g. BPH with overflow incontinence)

Epidemiology
- variable prevalence in women: 25-45%
- F:M = 2:1
- more frequent in the elderly, affecting 5-15% of those living in the community and 50% of nursing home residents

Table 3. Urinary Incontinence: Types and Treatments

<table>
<thead>
<tr>
<th>Type</th>
<th>Urgency</th>
<th>Stress</th>
<th>Mixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Involuntary leakage of urine preceded by a strong, sudden urge to void</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etiology</td>
<td>Bladder (detrusor overactivity)</td>
<td>Urethra/sphincter weakness, post-partum pelvic musculature weakness</td>
<td>Combination of bladder and sphincter issues</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hx</td>
<td>Hx</td>
<td>Hx</td>
</tr>
<tr>
<td>Urodynamics</td>
<td>Hx</td>
<td>Stress test (have patient bear down/cough)</td>
<td>Stress test</td>
</tr>
<tr>
<td>Therapy</td>
<td>Lifestyle changes (fluid alterations, diet, etc.)</td>
<td>Weight loss</td>
<td>Combination of management of urge and stress incontinence</td>
</tr>
<tr>
<td></td>
<td>Bladder habit training</td>
<td>Kegel exercises</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anticholinergics</td>
<td>Bulking agents</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β3 agonist</td>
<td>Surgery (slings, tension-free vaginal tape, transobturato tape, artificial sphincters)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Neurromodulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Botulinum toxin A</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Urgency is the symptom of a strong need to void; it is not necessarily associated with incontinence

Table 4. Etiology of Urinary Retention

<table>
<thead>
<tr>
<th>Outflow Obstruction</th>
<th>Bladder Innervation</th>
<th>Pharmacologic</th>
<th>Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bladder neck or urethra: calculus, clot, foreign body, neoplasm, neurologic (USD)</td>
<td>Intracranial: CVA, tumour, Parkinson’s, cerebral palsy</td>
<td>Anticholinergics</td>
<td>Gl: UTI, prostatitis, abscess, genital herpes</td>
</tr>
<tr>
<td>Prostate: BPH, prostate cancer</td>
<td>Spinal cord: injury, disc herniation, MS</td>
<td>Narcotics</td>
<td>Infected foreign body</td>
</tr>
<tr>
<td>Urethra: stricture, phimosis, traumatic disruption</td>
<td>DM</td>
<td>Antihypertensives (ganglionic blockers, methylidopa)</td>
<td>Varicella zoster</td>
</tr>
<tr>
<td>Miscellaneous: constipation, pelvic mass</td>
<td>Post-abdominal or pelvic surgery</td>
<td>OTC cold medications containing ephedrine or pseudoephedrine</td>
<td>Varicella zoster</td>
</tr>
</tbody>
</table>

Clinical Features
- suprapubic pain
- palpable and/or percussible bladder (suprapubic)
- possible purulent/bloody meatal discharge
- increased size of prostate or reduced anal sphincter tone on DRE
- neurological: presence of abnormal or absent deep tendon reflexes, reduced "anal wink", saddle anesthesia
**Investigations**
- CBC, electrolytes, Cr, BUN, U/A and urine C&S, U/S, cystoscopy, urodynamic studies, PVR

**Treatment**
- treat underlying cause
- catheterization
  - acute retention
    - immediate catheterization to relieve retention; leave Foley in to drain bladder; follow-up to determine cause; closely monitor fluid status and electrolytes (risk of POD)
  - chronic retention
    - intermittent catheterization by patient may be used; definitive treatment depends on etiology
- suprapubic tube placement
- for post-operative patients with retention:
  - encourage ambulation
  - α-blockers to relax bladder neck outlet
  - may need catheterization
  - definitive treatment will depend on etiology

---

**Benign Prostatic Hyperplasia**

**Definition**
- periurethral hyperplasia of stroma and epithelium in prostatic transition zone
- prostatic smooth muscle cells play a role in addition to hyperplasia

**Etiology**
- etiology unknown
  - DHT required (converted from testosterone by 5-α reductase)
  - possible role of impaired apoptosis, estrogens, other growth factors
  - genetic: increased risk in 1st degree relatives and twin studies

**Epidemiology**
- age-related, extremely common (50% of 50 yr olds, 80% of 80 yr olds)
- 25% of men will require treatment

**Clinical Features**
- result from outlet obstruction and compensatory changes in detrusor function
- voiding and storage symptoms
- DRE
  - prostate is smooth, rubbery, and symmetrically enlarged
- complications
  - retention
  - overflow incontinence
  - hydronephrosis
  - renal insufficiency
  - infection
  - gross hematuria
  - bladder stones

**Investigations**
- Hx, assessing LUTS and impact on QOL
  - may include self-administered questionnaires (IPSS or AUA symptom index for severity, progression, and treatment response)
- P/E, including DRE
- U/A to exclude UTI
- Cr to assess renal function
- renal U/S to assess for hydronephrosis
- PSA to rule out malignancy (see *Prostate Cancer Screening*, U25)
- uroflowmetry to measure flow rate (optional)
- PVR (optional)
- consider cystoscopy or transrectal ultrasound prior to potential surgical management to evaluate outlet and prostate volume
- biopsy if suspicious for malignancy, i.e. elevated PSA or abnormal DRE

---

*Approximate Prostate Sizes*
- 20 cc – chestnut
- 25 cc – plum
- 50 cc – lemon
- 75 cc – orange
- 100 cc – grapefruit

*Figure 7. Cross-section of prostate*

*Prostate size does not correlate well with symptoms in BPH*

*AUA BPH Symptom Score*

<table>
<thead>
<tr>
<th>FUNWISE</th>
</tr>
</thead>
<tbody>
<tr>
<td>F – Frequency</td>
</tr>
<tr>
<td>U – Urgency</td>
</tr>
<tr>
<td>N – Nocturia</td>
</tr>
<tr>
<td>W – Weak stream</td>
</tr>
<tr>
<td>I – Intermittency</td>
</tr>
<tr>
<td>S – Straining</td>
</tr>
</tbody>
</table>

*Each symptom graded out of 5
0-7: Mildly symptomatic
8-19: Moderately symptomatic
20-35: Severely symptomatic
Note: dysuria not included in score but is commonly associated with BPH*
Treatment

Table 5. Treatment of BPH

<table>
<thead>
<tr>
<th>When to use</th>
<th>Conservative</th>
<th>Medical</th>
<th>Surgical</th>
<th>Minimally Invasive Surgical Therapies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic patients</td>
<td>Moderate to severe symptoms that are distressing for patient</td>
<td>Significant symptom burden, acute urinary retention, refractory hematuria, recurrent infections</td>
<td>Patients who wish to avoid or may not tolerate surgery</td>
<td></td>
</tr>
<tr>
<td>Options</td>
<td>€ Watchful waiting: 50% of patients improve spontaneously € Lifestyle modifications (e.g. evening fluid restriction, planned voiding)</td>
<td>€ α-adrenergic antagonists: reduce stromal smooth muscle tone € 5-alpha reductase inhibitor: block conversion of testosterone to DHT; act to reduce prostate size € Combination is synergistic € Anti-cholinergic agents (for storage LUTS, without elevated PVR)</td>
<td>€ TURP (see U42) € Laser ablation € TUIP (prostate &lt; 30 g) € Open prostatectomy € Microwave therapy € TUNA € Prostatic stent (not commonly used)</td>
<td></td>
</tr>
</tbody>
</table>

Urethral Stricture

Definition
- Decrease in urethral calibre due to scar formation in urethra (may also involve corpus spongiosum)
- M>F

Etiology
- Congenital
  - Failure of normal canalization (i.e. posterior urethral valves)
- Trauma
  - Instrumentation/catheterization (most common)
  - External trauma (e.g. burns, straddle injury)
  - Foreign body
- Infection
  - Long-term indwelling catheter
  - STI (gonococcal or chlamydial disease)
- Inflammation
  - Balanitis xerotica obliterans (BXO; lichen sclerosis or chronic progressive sclerosing dermatosis of the male genitalia) causing meatal and urethral stenosis

Clinical Features
- Voiding symptoms
- Urinary retention
- Hydrenephrosis
- Related infections: recurrent UTI, secondary prostatitis/epididymitis

Investigations
- Laboratory findings
  - Flow rates <10 mL/s (normal ~20 mL/s) on uroflowmetry
  - Urine culture usually negative, but U/A may show pyuria
- Radiologic findings
  - RUG and VCUG will demonstrate location
- Cystoscopy

Treatment
- Urethral dilatation
  - Temporarily increases lumen size by breaking up scar tissue
  - Healing will often reform scar tissue, recurrence of stricture
- Visual internal urethrotomy (VIU)
- Endoscopically incise stricture
- Equal success rates to dilation with midbulbar strictures <2 cm
- High rate of recurrence (30-80%), avoid in younger patients
- Open surgical reconstruction
  - Complete stricture excision with anastomosis, ± urethroplasty depending on location and size of stricture

BPH Surgery

Absolute Indication
- Renal failure with obstructive uropathy
- Refractory urinary retention

Relative Indications
- Recurrent UTIs
- Recurrent hematuria refractory to medical treatment
- Renal insufficiency (rule out other causes)
- Bladder stones

BPH Surgery: Absolute Indication

- Men with planned cataract surgery should avoid starting α-adrenergic antagonists until after their surgery due to the risk of intraoperative floppy iris syndrome

Finasteride for Benign Prostatic Hyperplasia

Purpose: To examine the effectiveness and safety of finasteride versus placebo or other active controls for the treatment of urinary tract symptoms.

Summary of Findings:
1. Finasteride improved urinary symptoms more than placebo in trials >1 yr duration and significantly lowered the risk of BPH progression.
2. Compared with α-blockers, finasteride was less effective than either doxazosin or terazosin, but equally as effective as tamulosin.
3. Symptom improvement with finasteride + doxazosin is equal to doxazosin alone.
4. Finasteride treatment resulted in an increased risk of ejaculatory disorder, impotence and lowered libido compared with placebo.
5. Compared with doxazosin and tamulosin, finasteride had a lower risk of asthma, dizziness, and postural hypotension.

Microwave Thermotherapy for Benign Prostatic Hyperplasia

Purpose: To evaluate the efficacy and safety of microwave thermotherapy for the treatment of benign prostatic obstruction.

Selection Criteria: RCTs evaluating transurethral microwave therapy (TUMT) for men with symptomatic BPH with multiple comparison groups.

Results: 15 studies, 1,585 patients, mean age 66.8 yr, 3-60 mo duration. Mean urinary symptom scores decreased by 95% with TUMT and 77% with TURP.

The pooled mean peak urinary flow increased by 70% with TUMT and 119% with TURP. Compared with TURP, TUMT was associated with decreased risks for reoperation/splenorrhaphy, treatment for strictures, hematuria, blood transfusions and transurethral resection syndrome, but increased risk for dysuria, urinary retention and retreatment for BPH symptoms.

Conclusions: Overall, microwave thermotherapy techniques are effective alternatives to TURP and α-blockers for treating symptomatic BPH, although less effective than TURP in improving symptom score and urinary flow.
Neurogenic Bladder

Definition
• malfunctioning urinary bladder due to deficiency in some aspect of its innervation

Neurophysiology

Table 6. Efferent Sympathetic, Parasympathetic, and Somatic Nerve Supply

<table>
<thead>
<tr>
<th>Nerve Fibres</th>
<th>Nerve Roots</th>
<th>Neurotransmitter/Receptor</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sympathetic</td>
<td>T10-L2</td>
<td>NA/Adrenergic</td>
<td>Trigone, internal sphincter, proximal urethra (c) Bladder body (l)</td>
</tr>
<tr>
<td>Somatic (Pudendal)</td>
<td>S2-4</td>
<td>ACh/Nicotinic</td>
<td>External sphincter</td>
</tr>
<tr>
<td>Parasympathetic</td>
<td>S2-4</td>
<td>ACh/Muscarinic (M2, M3)</td>
<td>Detrusor</td>
</tr>
</tbody>
</table>

• stretch receptors in the bladder wall relay information to PMC and activate micturition reflex (normally inhibited by cortical input)
  • micturition
    • stimulation of parasympathetic neurons (bladder contraction)
    • inhibition of sympathetic and somatic neurons (internal and external sphincter relaxation, respectively)
  • urine storage
    • opposite of micturition
• voluntary action of external sphincter (pudendal nerve roots S2-S4) can inhibit urge to urinate
• cerebellum, basal ganglia, thalamus, and hypothalamus all have input at PMC in the brainstem

Classification of Neurologic Voiding Dysfunction
• neuropathic detrusor overactivity (formerly termed detrusor hyperreflexia)
  • lesion above PMC (e.g. stroke, tumour, MS, Parkinson’s disease)
  • loss of voluntary inhibition of voiding
  • intact pathway inferior to PMC maintains coordination of bladder and sphincter
• detrusor sphincter dyssynergia (DSD)
  • suprasacral lesion of spinal cord (e.g. trauma, MS, arteriovenous malformation, transverse myelitis)
  • loss of coordination between detrusor and sphincter (detrusor contracts on closed sphincter and vice versa)
• component of detrusor overactivity as well
• detrusor atony/areflexia
  • lesion of sacral cord or peripheral efferents (e.g. trauma, DM, disc herniation, MS, congenital spinal cord abnormality, post abdominoperineal resection)
  • flaccid bladder which fails to contract
  • may progress to poorly compliant bladder with high pressures
• peripheral autonomic neuropathy
  • deficient bladder sensation → increasing residual urine → decompensation (e.g. DM, neurosyphilis, herpes zoster)
• muscular lesion
  • can involve detrusor, smooth/striated sphincter

Neuro-Urologic Evaluation
• Hx and P/E (urologic and general neurologic)
• U/A, renal profile
• imaging
  • IVP (less used), U/S to rule out hydronephrosis and stones
• cystoscopy
• urodynamic studies
  • uroflowmetry to assess flow rate, pattern
  • filling CMG to assess capacity, compliance, detrusor overactivity
  • voiding CMG (pressure-flow study) to assess bladder contractility and extent of bladder outlet obstruction
  • video study to visualize bladder/bladder neck/urethra during CMG using x-ray contrast
• EMG ascertains presence of coordinated or uncoordinated voiding, allows accurate diagnosis of DSD

Treatment
• goals of treatment
  • prevent renal failure
  • prevent infections
  • achieve social continence
• clean intermittent catheterization (CIC)
• treatment options depend on status of bladder and urethra
  • bladder hyperactivity → anticholinergic medications to relax bladder (see Urinary Incontinence, U5)
    • if refractory
      – botulinum toxin injections into bladder wall
      – occasionally augmentation cystoplasty (enlarging bladder volume and improving compliance by grafting section of detubularized bowel onto the bladder)
      – occasionally urinary diversion (ileal conduit or continent diversion) in severe cases if bladder management unsuccessful
  • flaccid bladder → CIC

### Dysuria

**Definition**
- painful urination

**Etiology**

<table>
<thead>
<tr>
<th>Table 7. Differential Diagnosis of Dysuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
</tr>
<tr>
<td>Neoplasm</td>
</tr>
<tr>
<td>Calculi</td>
</tr>
<tr>
<td>Inflammatory</td>
</tr>
<tr>
<td>Hormonal</td>
</tr>
<tr>
<td>Trauma</td>
</tr>
<tr>
<td>Psychogenic</td>
</tr>
<tr>
<td>Other</td>
</tr>
</tbody>
</table>

**Investigations**
- focused Hx and P/E to determine cause (fever, d/c, conjunctivitis, CVA tenderness, back/joint pain)
  - any d/c (urethral, vaginal, cervical) should be sent for gonococcus/chlamydia testing; wet mount if vaginal d/c
  - U/A and urine C&S
  - if suspect infection, may start empiric ABx treatment (see Table 8, U11)
  - ± imaging of urinary tract (tumour, stones)

### Hydronephrosis

**Definition**
- dilation of the renal pelvis and calyces caused by the impairment in antegrade urine flow

**Etiology**
- mechanical
  - congenital: see Congenital Abnormalities, U35
  - acquired
    - intrinsic: trauma, inflammation and bleeding, calculi, urologic neoplasms, BPH, urethral stricture, phimosis, previous urological surgery
    - extrinsic: trauma, neoplasms (uterine fibroid, colorectal, uterine, and cervical malignancies; lymphoma), aortic aneurysm, pregnancy (gravid uterus)
  - functional
    - neuropathic: neurogenic bladder, diabetic neuropathy, spinal cord disease
    - pharmacologic: anticholinergics, α-adrenergic agonists
    - hormonal: pregnancy (progesterone decreases ureteral tone)

**Investigations**
- focused Hx, inquiring about pain (flank, lower abdomen, testes, labia), U/O, medication use, pregnancy, trauma, fever, Hx of UTIs, calculi, and PID and urological surgery
• CBC, electrolytes, Cr, BUN, U/A, C&S
• imaging studies (U/S is >90% sensitive and specific)
  ▪ MAG3 diuretic renogram: evaluates differential renal function and demonstrates if functional obstruction exists

**Treatment**
• hydrenephrosis can be physiologic
• treatment should be guided at improving symptoms, treating infections, or improving renal function
• urgent treatment may require percutaneous nephrostomy tube or ureteral stenting to relieve pressure

---

**Post-Obstructive Diuresis**

**Definition**
• polyuria resulting from relief of severe chronic obstruction
• >3 L/24 h or >200 cc/h over each of two consecutive hours

**Pathophysiology**
• **physiologic POD** secondary to excretion of retained urea, Na⁺, and H₂O (high osmotic load) after relief of obstruction
  ▪ self-limiting; usually resolves in 48 h with PO fluids but may persist to pathologic POD
• **pathologic POD** is a Na⁺-wasting nephropathy secondary to impaired concentrating ability of the renal tubules due to
  ▪ decreased reabsorption of NaCl in the thick ascending limb and urea in the collecting tubule
  ▪ increased medullary blood flow (solute washout)
  ▪ increased flow and solute concentration in the distal nephrons

**Management**
• admit patient and closely monitor hemodynamic status and electrolytes (Na⁺ and K⁺ q6-12h and replace prn; follow Cr and BUN to baseline)
• monitor U/O q2h and ensure total fluid intake <U/O by replacing every 1 mL U/O with 0.5 mL 1/2 NS IV (PO fluids if physiologic POD)
• avoid glucose-containing fluid replacement (iatrogenic diuresis)

---

**Overactive Bladder**

**Definition**
• a symptom complex that includes urinary urgency with or without urgency incontinence, urinary frequency (voiding >8 times in a 24 hr period), and nocturia (awakening two or more times at night to void)

**Etiology**
• etiology unknown
• symptoms usually associated with involuntary contractions of the detrusor muscle. The overactivity of the muscle could be neurogenic, myogenic or idiopathic

**Epidemiology**
• F:M= 1:1
• prevalence increases with age. 42% in males 75 years old or older; 31% in females 75 years old or older

**Diagnosis**
• the diagnostic process should document symptoms and signs that define overactive bladder and exclude other disorders that could cause of the patient’s symptoms
• minimal requirements for the process consist of
  ▪ focused history including past genitourinary disorders and conditions outlined in Table 8, questionnaires of LUTS for women and diaries of urination frequency, volume and pattern
  ▪ P/E including genitourinary, pelvic and rectal examination
  ▪ urinalysis to rule out hematuria and infection
  ▪ in some patients, the following investigations could be considered
    ▪ bladder scan for residual urine in patients with risk factors of urinary retention
    ▪ cystoscopy to rule out recurrent infections, carcinoma in situ and other intravesical abnormalities
    ▪ urodynamics to rule out obstruction in older men
Treatment

- **non-pharmacological**: behaviour therapies such as bladder training, bladder control strategies, pelvic floor muscle training, fluid management, and avoidance of caffeine
- **pharmacological**
  - anti-muscarinics such as oxybutinin hydrochloride, tolterodine, solifenacin, fesoterodine, or trospium
  - β3-adrenoceptor agonist such as mirabegron
- refractory patients may be treated with
  - neuromuscular-junction inhibition such as botulinum toxin bladder injection
- other interventional procedures include
  - posterior tibial nerve stimulation (not used commonly in Canada)
  - sacral neuromodulation

Table 8. Conditions that could contribute to symptoms of Overactive Bladder

<table>
<thead>
<tr>
<th>Condition</th>
<th>UTI, obstruction, impaired bladder contractility</th>
<th>Stroke, MS, dementia, diabetic neuropathy</th>
<th>CHF, sleep disorders (primarily nocturia)</th>
<th>Excessive caffeine and alcohol, constipation, impaired mobility</th>
<th>Diuretics, anticholinergic agents, narcotics, calcium-channel blocker, cholinesterase inhibitors</th>
</tr>
</thead>
</table>

### Infectious and Inflammatory Diseases

#### Table 8. Antibiotic Treatment of Urological Infections

<table>
<thead>
<tr>
<th>Condition</th>
<th>Drug</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urethritis</td>
<td>Non-Gonococcal azithromycin (1 g PO)</td>
<td>x 1</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>doxycycline (100 mg PO bid)</td>
<td>7 d</td>
</tr>
<tr>
<td>Gonococcal</td>
<td>ceftriaxone (250 mg IM) AND treat for Chlamydia trachomatis</td>
<td>x 1</td>
</tr>
<tr>
<td>Simple, Uncomplicated UTI</td>
<td>TMP-SMX (160 mg/800 mg PO bid)</td>
<td>3 d</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nitrofurantoin (100 mg PO bid)</td>
<td>5 d</td>
</tr>
<tr>
<td>Complicated UTI</td>
<td>ciprofloxacin (1 g PO daily OR 400 mg IV q12h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ampicillin (1 g IV q6h) + gentamicin (1 mg/kg IV q8h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td></td>
<td>OR</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ceftriaxone (1-2 g IV q24h)</td>
<td>up to 2-3 wk</td>
</tr>
<tr>
<td>Recurrent/Chronic Cystitis</td>
<td>rophylactic treatment</td>
<td></td>
</tr>
<tr>
<td>Continuous:</td>
<td>TMP-SMX (40 mg/200 mg PO qd OR 3x/wk)</td>
<td>6-12 mo</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrofurantoin (50-100 mg PO qd)</td>
<td></td>
<td>6-12 mo</td>
</tr>
<tr>
<td>Post-Coital:</td>
<td>TMP-SMX (40 mg/200 mg-80 mg/400 mg)</td>
<td>within 2 h of coitus</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>nitrofurantoin (50-100 mg PO qd)</td>
<td></td>
<td>within 2 h of coitus</td>
</tr>
<tr>
<td>Acute Prostatitis</td>
<td>ciprofloxacin (500-750 mg PO bid)</td>
<td>2-4 wk</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TMP-SMX (160 mg/800 mg PO bid)</td>
<td></td>
<td>4 wk</td>
</tr>
<tr>
<td>OR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IV therapy with gentamicin and ampicillin with β-lactamase inhibitor; 3rd gen cephalosporin, OR a fluoroquinolone</td>
<td>4 wk total (IV and oral step-down)</td>
<td></td>
</tr>
<tr>
<td>Chronic Prostatitis</td>
<td>ciprofloxacin (500 mg PO bid)</td>
<td>4-6 wk</td>
</tr>
<tr>
<td>Epididymitis/Orchitis</td>
<td>&lt;35 yr ceftriaxone (200 mg IM) AND doxycycline (100 mg PO bid)</td>
<td>x 1</td>
</tr>
<tr>
<td>≥35 yr</td>
<td>oxoflaxacin (300 mg PO bid)</td>
<td>10 d</td>
</tr>
<tr>
<td>Acute Uncomplicated Pyelonephritis</td>
<td>ciprofloxacin (500 mg PO bid)</td>
<td>7 d</td>
</tr>
<tr>
<td>≥ ceftriaxone (1 g IV) OR ciprofloxacin (400 mg IV)</td>
<td>x 1</td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>IV therapy with a fluoroquinolone, gentamicin and ampicillin, extended spectrum cephalosporin, OR a carbapenem</td>
<td>14 d total (IV and oral step-down)</td>
</tr>
</tbody>
</table>

Antibiotic therapy should always be based on local resistance patterns and adjusted according to culture and sensitivity results.

Cystitis: Common Pathogens

**KEEPS**
- Klebsiella sp.
- E. coli (90%), other Gram-negatives
- Enterococci
- Proteus mirabilis, Pseudomonas
- S. saprophyticus

Acute uncomplicated pyelonephritis: suspected or confirmed enterococcus infection requires treatment with ampicillin.
Urinary Tract Infection

- for UTIs during pregnancy, see Obstetrics, OB29

**Definition**
- symptoms suggestive of UTI + evidence of pyuria and bacteriuria on U/A or urine C&S
  - if asymptomatic + 100,000 CFU/mL = asymptomatic bacteriuria; only requires treatment in certain patients (e.g. pregnancy)

**Classification**
- uncomplicated: lower UTI in a setting of functionally and structurally normal urinary tract
- complicated: structural and/or functional abnormality, male patients, immunocompromised, diabetic, iatrogenic complication, pregnancy, pyelonephritis, catheter-associated
- recurrent: see Recurrent/Chronic Cystitis

**Risk Factors**
- stasis and obstruction
  - residual urine due to impaired urine flow e.g. PUVs, reflux, medication, BPH, urethral stricture, cystocele, neurogenic bladder
- foreign body
  - introduce pathogen or act as nidus of infection e.g. catheter, instrumentation
- decreased resistance to organisms
  - DM, malignancy, immunosuppression, spermicide use, estrogen depletion, antimicrobial use
- other factors
  - trauma, anatomic abnormalities, female, sexual activity, fecal incontinence

**Clinical Features**
- storage symptoms: frequency, urgency, dysuria
- voiding symptoms: hesitancy, post-void dribbling
- other: suprapubic pain, hematuria, foul-smelling urine
- pyelonephritis – if present: typically presents with more severe symptoms (e.g. fever/chills, CVA tenderness, flank pain)

**Organisms**
- typical organisms
- atypical organisms
  - tuberculosis (TB)
  - *Chlamydia trachomatis*
  - Mycoplasma (*Ureaplasma urealyticum*)
  - fungi (Candida)

**Indications for Investigations**
- pyelonephritis
- persistence of pyuria/symptoms following adequate antibiotic therapy
- severe infection with an increase in Cr
- recurrent/persistent infections
- atypical pathogens (urea splitting organisms)
- Hx of structural abnormalities/decreased flow

**Investigations**
- U/A, urine C&S
  - UA: leukocytes ± nitrites ± hematuria
  - C&S: midstream, catheterized, or suprapubic aspirate
- if hematuria present, retest post-treatment, if persistent need hematuria workup (see Microscopic Hematuria, US)
- U/S, CT scan if indicated

**Treatment**
- see Table 8 for approach to ABx therapy
- if febrile, consider admission with IV therapy and rule out obstruction

**Prevention of UTIs**
- Maintain good hydration (try cranberry juice)
- Wipe from front to back to avoid contamination of the urethra with feces from the rectum
- Avoid feminine hygiene sprays and scented douches
- Empty bladder immediately before and after intercourse
Recurrent/Chronic Cystitis

Definition
• ≥3 UTIs/yr

Etiology
• bacterial reinfection (80%) vs. bacterial persistence (relapse)
  ▪ bacterial reinfection
    • recurrence of infection with either 1) a different organism, 2) the same organism if cultured >2 wk following therapy, or 3) with any organism with an intermittent sterile culture
  ▪ bacterial persistence
    • same organism cultured within 2 wk of sensitivity-based therapy

Investigations
• assess predisposing factors as described above
• investigations may include cystoscopy, U/S, CT

Treatment
• lifestyle changes (limit caffeine intake, increase fluid/H2O intake)
• ABx: continuous vs. post-coital
• post-menopausal women: consider topical or systemic estrogen therapy
• no treatment for asymptomatic bacteriuria except in pregnant women or patients undergoing urinary tract instrumentation

Interstitial Cystitis
(Painful Bladder or Bladder Pain Syndrome)

Definition
• bladder pain, chronic urgency and frequency without other reasonable causation

Classification
• non-ulcerative (more common)
• ulcerative

Etiology
• unknown
  ▪ theories: increased epithelial permeability, autoimmune, neurogenic, defective GAG layer overlying mucosa
  ▪ associations: severe allergies, IBS, fibromyalgia

Epidemiology
• prevalence: 20/100,000
• 90% of cases are in females
• mean age at onset is 40 yr (non-ulcerative tends to affect a younger to middle-aged population, while ulcerative tends to be seen in middle-aged to older)

Clinical Features
• pain associated with the bladder
• glomerulations (submucosal petechiae) or Hunner’s lesions (ulcers) on cystoscopic examination
• urinary urgency
• negative U/A, urine C&S, and urine cytology

Differential Diagnosis
• UTI, vaginitis, bladder tumour
• radiation/chemical cystitis
• eosinophilic/TB cystitis
• bladder calculi

Treatment
• first-line: patient empowerment (diet, lifestyle, stress management), pain management
• second-line
  ▪ oral: pentosan polysulfate sodium, amitriptyline, cimetidine, hydroxyzine
  ▪ intravesical: dimethylsulfoxide (DMSO), heparin, lidocaine
• third-line: cystoscopy with bladder hydrodistention (traditionally diagnostic) under GA, treat Hunner’s lesions if present
• other: neuromodulation, cyclosporine A, intradetrusor botulinum toxin
• surgery (last resort): augmentation cystoplasty, or urinary diversion ± cystectomy

Four Symptom Scores Exist to Evaluate and Monitor Patients with Interstitial Cystitis
• Interstitial Cystitis Symptom Index (ICSI)
• Interstitial Cystitis Problem Index (ICPI)
• Wisconsin Interstitial Cystitis (UW-IC) Scale
• Pain, Urgency and Frequency (PUF) Score

Cystoscopic evaluation is not necessary to make a diagnosis
**Acute Pyelonephritis**

**Definition**
- infection of the renal parenchyma with local and systemic manifestations
- clinical diagnosis of flank pain, fever and elevated WBC

**Etiology**
- ascending (usually GN bacilli) or hematogenous route (usually GP cocci)
- causative microorganisms
  - gram positives: *Enterococcus faecalis, S. aureus, S. saprophyticus*
  - gram negatives: *E. coli* (most common), *Klebsiella, Proteus, Pseudomonas, Enterobacter*
- common underlying causes of pyelonephritis
  - stones, strictures, prostatic obstruction, vesicoureteric reflux, neurogenic bladder, catheters, DM, sickle-cell disease, PCKD, immunosuppression, post-renal transplant, instrumentation, pregnancy

**Clinical Features**
- rapid onset (<24 h)
- LUTS including frequency, urgency, hematuria; NOT dysuria unless concurrent cystitis
- fever, chills, nausea, vomiting, myalgia, malaise
- CVA tenderness or exquisite flank pain

**Investigations**
- U/A, urine C&S
- CBC and differential: leukocytosis, left shift
- imaging indicated if suspicious of complicated pyelonephritis or symptoms do not improve with 48-72 h of treatment
  - abdominal/pelvic U/S
  - CT
- nuclear medicine: DMSA scan can be used to help secure the diagnosis
  - a photopenic defect indicates active infection or scar; if normal alternative diagnoses should be considered

**Treatment**
- hemodynamically stable
  - outpatient oral ABx treatment ± single initial IV dose (see Table 9)
- severe or non-resolving
  - admit, hydrate, and treat with IV ABx (see Table 9)
- emphysematous pyelonephritis
  - percutaneous nephrostomy tube and antibiotics first line
  - consider early nephrectomy after IV ABx started and patient stabilized
- renal obstruction
  - admit for emergent stenting or percutaneous nephrostomy tube

**Prostatitis/Prostatodynia**

**Epidemiology**
- most common urologic diagnosis in men <50 yr
- prevalence 2-12%

---

Nitrofurantoin has poor tissue penetration and therefore is not used to treat pyelonephritis (requires post-renal uroconcentration)
### Classification

#### Table 10. Comparison of the Three Types of Prostatitis

<table>
<thead>
<tr>
<th>Category I: Acute Bacterial Prostatitis</th>
<th>Category II: Chronic Bacterial Prostatitis</th>
<th>Category III: Chronic Pelvic Pain Syndrome (CPPS) (Abacterial)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etiology</strong></td>
<td>Recurrent exacerbations of acute prostatitis-like signs and symptoms</td>
<td>Divided into inflammatory (IIIA) and non-inflammatory (IIIB)</td>
</tr>
<tr>
<td>Ascending urethral infection with KEEP (see U12 sidebar): 80% E. coli</td>
<td>Recurrent UTI with same organism</td>
<td>Intraprostatic reflux of urine ± urethral hypertonia</td>
</tr>
<tr>
<td>Often associated with outlet obstruction, recent cystoscopy, prostatic biopsy</td>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain</td>
<td>Multifactorial (immunological, neuropathic, neuroendocrine, psychosocial)</td>
</tr>
<tr>
<td>Most infections occur in the peripheral zone (see Figure 7, U7)</td>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain</td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td>Same as per Category II</td>
<td></td>
</tr>
<tr>
<td>Acute onset fever, chills, malaise, Rectal, lower back, and perineal pain LUTS</td>
<td>NIH-CPSI score*</td>
<td></td>
</tr>
<tr>
<td>Pelvic pain, storage LUTS, ejaculatory pain, post-ejaculatory pain</td>
<td>Consider psychological assessment</td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>P/E: abdomen, external genitalia, perineum, prostate U/A</td>
<td>Supportive measures PO or IV ABx depending how sick (see Table 9) Supportive measures Trial of ABx therapy if newly diagnosed</td>
<td>Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess, or epididymo-orchitis</td>
</tr>
<tr>
<td>Blood CBC, C&amp;S</td>
<td>May consider catheterization in patients with severe obstructive LUTS or retention I&amp;D of abscess if present</td>
<td>Consider addition of an α-blocker</td>
</tr>
<tr>
<td>Transrectal U/S if non-resolving/ suspect prostatic abscess</td>
<td>ABx (see Table 9)</td>
<td>Anti-inflammatories</td>
</tr>
<tr>
<td></td>
<td>Urine C&amp;S: 4-glass test VB1 (voided bladder): initial (urethra) VB2: midstream (bladder) EPS (expressed prostatic secretions): not usually performed VB3: post-massage/DRE</td>
<td>Phytotherapy (quercetin, cernilton)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>Epididymitis and Orchitis</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td><strong>Etiology</strong></td>
<td>Rule out torsion (see Investigations Table 24, U29)</td>
<td>Prostatic massage may cause extreme tenderness and increased risk of inducing sepsis, abscess, or epididymo-orchitis</td>
</tr>
<tr>
<td>• common infectious causes</td>
<td>see Table 9 for ABx therapy</td>
<td></td>
</tr>
<tr>
<td>• &lt;35 yr: N. gonorrhoeae or Chlamydia trachomatis</td>
<td>scrotal support, bed rest, ice, analgesia</td>
<td></td>
</tr>
<tr>
<td>• ≥35 yr or penetrative anal intercourse: GI organisms (especially E. coli)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• other causes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• mumps infection may involve orchitis, post-parotitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• syphilis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• granulomatous (autoimmune) in elderly men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• amiodarone (involves only head of epididymis)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• chemical: reflux of urine into ejaculatory ducts</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• UTI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• unprotected sexual contact</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• instrumentation/catherization</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• increased pressure in prostatic urethra (straining, voiding, heavy lifting) may cause reflux of urine along vas deferens → sterile epididymitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• immunocompromise</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Clinical Features</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• sudden onset scrotal pain and swelling ± radiation along cord to flank</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• scrotal erythema and tenderness</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• fever</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• storage symptoms, purulent d/c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• reactive hydrocele</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Investigations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• U/A, urine C&amp;S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• ± urethral d/c: Gram stain/culture</td>
<td>If unsure between diagnoses of epididymitis and torsion, always go to OR</td>
<td></td>
</tr>
<tr>
<td>• if diagnosis uncertain, must do</td>
<td>Remember: torsion &gt;6 h has poor prognosis</td>
<td></td>
</tr>
<tr>
<td>• colour-flow Doppler U/S to rule out testicular torsion</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• rule out torsion (see Investigations Table 24, U29)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• see Table 9 for ABx therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• scrotal support, bed rest, ice, analgesia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Complications
• if severe → testicular atrophy
• 30% have persistent infertility problems

Urethritis

Etiology
• infectious or inflammatory (e.g. reactive arthritis)

Table 11. Infectious Urethritis: Gonococcal vs. Non-Gonococcal

<table>
<thead>
<tr>
<th>Causative Organism</th>
<th>Gonococcal</th>
<th>Non-Gonococcal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neisseria gonorrhoeae</td>
<td></td>
<td>Usually Chlamydia trachomatis</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Hx of sexual contact, thick, profuse, yellow-grey purulent d/c, LUTS</td>
<td>Hx of sexual contact, mucoid whitish purulent d/c, ± storage LUTS</td>
</tr>
<tr>
<td></td>
<td>Gram stain (GN diplococci), urine PCR and/or culture from urethral specimen</td>
<td>Gram stain demonstrates &gt;4 PMN/oil immersion field, no evidence of N. gonorrhoeae, urine PCR and/or culture from urethral specimen</td>
</tr>
</tbody>
</table>

Treatment
See Table 9

Stone Disease

Epidemiology
• prevalence of 2-3%
• M:F = 3:1
• peak incidence 30-50 yr of age
• recurrence rate: 10% at 1 yr, 50% at 5 yr, 60-80% lifetime

Risk Factors
• hereditary: RTA, Glucose-6-phosphate dehydrogenase deficiency, cystinuria, xanthinuria, oxaluria, etc.
• lifestyle: minimal fluid intake; excess vitamin C, oxalate, purines, calcium
• medications: loop diuretics (furosemide, bumetanide), acetazolamide, topiramate, and zonisamide
• medical conditions: UTI (with urea-splitting organisms: Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus), myeloproliferative disorders, IBD, gout, DM, hypercalcemia disorders (hyperparathyroidism, tumour lysis syndrome, sarcoidosis, histoplasmosis), obesity (BMI >30)

Clinical Features
• urinary obstruction → upstream distention → pain
  ▪ flank pain from renal capsule distention (non-colicky)
  ▪ severe waxing and waning pain radiating from flank to groin, testis, or tip of penis due to stretching of collecting system or ureter (ureteral colic)
• writhing, never comfortable, nausea, vomiting, hematuria (90% microscopic), diaphoresis, tachycardia, tachypnea
• occasionally symptoms of trigonal irritation (frequency, urgency)
• bladder stones result in: storage and voiding LUTS, terminal hematuria, suprapubic pain
• if fever, rule out concurrent pyelonephritis and/or obstruction

Table 12. Differential Diagnosis of Renal Colic

<table>
<thead>
<tr>
<th>GU</th>
<th>Abdominal</th>
<th>Neurological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyelonephritis</td>
<td>AAA</td>
<td>Radiculitis (L1): herpes zoster, nerve root compression</td>
</tr>
<tr>
<td>Ureteral obstruction from other cause: UPJ obstruction, clot colic secondary to gross hematuria, sloughed papillae</td>
<td>Bowel ischemia</td>
<td></td>
</tr>
<tr>
<td>Gynecological: ectopic pregnancy, torsion/rupture of ovarian cyst, PID</td>
<td>Pancreatitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other acute abdominal crisis</td>
<td></td>
</tr>
</tbody>
</table>

Location of Stones
• calyx: may cause flank discomfort, persistent infection, persistent hematuria, or remain asymptomatic
• pelvis: tend to cause obstruction at UPJ, may cause persistent infection
• ureter: <5 mm diameter will pass spontaneously in 75% of patients

Stone Pathogenesis
• supersaturation of stone constituents (at appropriate temperature and pH)
• stasis, low flow, and low volume of urine (dehydration)
• crystal formation and stone nidus
• loss of inhibitory factors
  ▪ citrate (forms soluble complex with calcium)
  ▪ magnesium (forms soluble complex with oxalate)
  ▪ pyrophosphate
  ▪ Tamm-Horsfall glycoprotein

Radiopaque Radiolucent

<table>
<thead>
<tr>
<th>Radiopaque</th>
<th>Radiolucent</th>
</tr>
</thead>
<tbody>
<tr>
<td>KUB Calcium</td>
<td>Uric acid</td>
</tr>
<tr>
<td>Struvite Cystine</td>
<td>Indinavir Atazanavir</td>
</tr>
<tr>
<td>CT Calcium</td>
<td>Indinavir</td>
</tr>
<tr>
<td>Struvite Cystine</td>
<td>Atazanavir</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
</tr>
</tbody>
</table>
### Approach to Renal Stones

![Diagram of Approach to Renal Stones](image)

**Figure 8. Approach to renal stone**

### Investigations

**Table 13. Investigations for Renal Stones**

<table>
<thead>
<tr>
<th>CBC, Uric Acid, U/A, Urine C&amp;S</th>
<th>KUB x-ray</th>
<th>CT Scan</th>
<th>Abdominal Ultrasound</th>
<th>Cystoscopy</th>
<th>PTH, 24 h urine x 2 for volume, Ca, Ca²⁺, Na⁺, PO₄³⁻, Mg²⁺, oxalate, citrate, ± cystine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Who gets it?</td>
<td>Everyone</td>
<td>Most</td>
<td>First episode renal colic</td>
<td>Pedietic cases or those concerning for obstruction</td>
<td>± Those concerning for bladder stone</td>
</tr>
<tr>
<td>Why is it done?</td>
<td>May show signs of infection, ± sensitivities</td>
<td>90% of stones are radiopaque, Good for follow-up</td>
<td>Distinguish radiolucent stone from soft tissue filling defect X-ray comparison</td>
<td>Identify and follow-up stone without radiation exposure Visualize hydronephrosis</td>
<td>Visualize bladder Need to rule out metabolic cause for stones</td>
</tr>
<tr>
<td>Cautions</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Who gets it?**
- Everyone
- Most
- First episode renal colic
- Pediatric cases or those concerning for obstruction
- ± Those concerning for bladder stone
- Recurrent Ca²⁺ stone formers
- ± pediatric cases

**Why is it done?**
- May show signs of infection, ± sensitivities
- 90% of stones are radiopaque, Good for follow-up
- Distinguish radiolucent stone from soft tissue filling defect X-ray comparison
- Identify and follow-up stone without radiation exposure Visualize hydronephrosis
- Visualize bladder Need to rule out metabolic cause for stones

**Cautions**
- – Do not mistake phleboliths for stones!
- Radiation (especially if female of child bearing age) Must be a non-contrast scan
- Not good at visualizing stones in ureter
- – –

**Who gets it?**
- Everyone
- Most
- First episode renal colic
- Pediatric cases or those concerning for obstruction
- ± Those concerning for bladder stone
- Recurrent Ca²⁺ stone formers
- ± pediatric cases

**Why is it done?**
- May show signs of infection, ± sensitivities
- 90% of stones are radiopaque, Good for follow-up
- Distinguish radiolucent stone from soft tissue filling defect X-ray comparison
- Identify and follow-up stone without radiation exposure Visualize hydronephrosis
- Visualize bladder Need to rule out metabolic cause for stones

**Cautions**
- – Do not mistake phleboliths for stones!
- Radiation (especially if female of child bearing age) Must be a non-contrast scan
- Not good at visualizing stones in ureter
- – –

### Treatment – Acute

- **Medical**
  - analgesic ± antiemetic
  - NSAIDs help lower intra-ureteral pressure
  - medical expulsion therapy (MET)
  - α-blockers: increase rate of spontaneous passage in distal ureteral stones
  - calcium channel blockers
  - ± Abx for bacteriuria
  - IV fluids if vomiting (note: IV fluids do NOT promote stone passage)
- **Interventional**
  - required if obstruction endangers patient, e.g. sepsis, renal failure
  - first line: ureteric stent (via cystoscopy)
  - second line: image-guided percutaneous nephrostomy
- admit if necessary
  - **Indications for Admission to Hospital**

### Treatment – Elective

- **Medical**
  - likely conservative if ureteral stone <10 mm or kidney stone <5 mm and no complications/symptoms well controlled
  - stones <5 mm especially likely to pass spontaneously
  - PO fluids to increase urine volume to >2 L/d (3-4 L if cystine) and MET
  - specific to stone type (see Table 14)
  - periodic imaging to monitor stone position and assess for hydronephrosis
  - progress to interventional stone removal methods if symptoms worsen or fail to improve (indicating stone passage)

**Indications for Admission to Hospital**
- Intractable pain
- Intractable vomiting
- Fever (suggests infection)
- Compromised renal function (including single kidney, bilateral obstructing stone)
- Pregnancy

**Detailed metabolic studies are NOT recommended unless complex patient (recurrent stone formers, pregnancy, pediatrics, strong family Hx, underlying kidney or systemic disease, etc.)**
• interventional
  • kidney
    - may stent prior to ESWL if stone is 1.5-2.5 cm
    - ESWL if stone <2 cm
    - PCNL if stone >2 cm
  • ureteral stones >10 mm
  • ESWL and URS are both first line treatment modalities for all locations
    - URS has significantly greater stone-free rates for stones at all locations in ureter, but also has higher complication rates (ureter perforation, stricture formation, etc.)
  • PCNL is second line treatment
  • laparoscopic or open stone removal (very rare)
  • bladder
    - transurethral stone removal or cystolitholapaxy
    - remove outflow obstruction (TURP or stricture dilatation)

Prevention
• dietary modification
  - increase fluid (>2 L/d), K+ intake
  - reduce animal protein, oxalate, Na+, sucrose, and fructose intake
  - avoid high-dose vitamin C supplements
  - thiazide diuretics for hypercalciuria
  - allopurinol for hyperuricosuria
  - potassium citrate for hypocitraturia, hyperuricosuria

Table 14. Stone Classification

<table>
<thead>
<tr>
<th>Type of Stone</th>
<th>Calcium (75-85%)</th>
<th>Uric Acid (5-10%)</th>
<th>Struvite (5-10%)</th>
<th>Cystine (1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etiology</td>
<td>Hypercalciuria</td>
<td>Hyperuricosuria (25% of patients with Ca²⁺ stones)</td>
<td>Urac acid precipitates in low volume, acidic urine with a high uric acid concentration:</td>
<td>Infection with urea-splitting organisms (Proteus, Pseudomonas, Providencia, Klebsiella, Mycoplasma, Serratia, S. aureus) results in alkaline urinary pH and precipitation of struvite (magnesium ammonium phosphate)</td>
</tr>
<tr>
<td></td>
<td>Hyperoxaluria (&lt;5% of patients)</td>
<td>Hyperparathyroidism, obesity, gout, DM</td>
<td>Hyperuricosuria alone</td>
<td>Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in “COLA” in urine (cystine, ornithine, lysine, arginine)</td>
</tr>
<tr>
<td></td>
<td>Hypocitraturia (12% of patients)</td>
<td>High dietary Na⁺</td>
<td>Low urinary pH, low urine volume (e.g. GI water loss)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Other causes:</td>
<td>Decreased urinary proteins</td>
<td>Drugs (ASA, thiazides)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hypomagnesemia – associated with hyperoxaluria and hypocitraturia</td>
<td>High urinary pH, low urine volume (e.g. GI water loss)</td>
<td>Diet (purine rich red meats)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High dietary Na⁺</td>
<td>Hyperuricosuria with hyperuricosuria</td>
<td>Hyperuricosuria with hypercalciuria</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Decreased urinary proteins</td>
<td>Gout</td>
<td>Gout</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• High urinary pH, low urine volume (e.g. GI water loss)</td>
<td>High rate of cell turnover or cell death (leukemia, cystotoxic drugs)</td>
<td>High rate of cell turnover or cell death (leukemia, cystotoxic drugs)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Hyperparathyroidism, obesity, gout, DM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Key Features</td>
<td>Radiopaque on KUB</td>
<td>Radiopaque on KUB</td>
<td>Radiopaque on KUB</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reducing dietary Ca²⁺ is NOT an effective method of prevention/treatment</td>
<td>Radiopaque on CT</td>
<td>Radiopaque on CT</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acidic urine, pH &lt;5.5 (NOT necessarily elevated urinary uric acid)</td>
<td>Acidic urine, pH &lt;5.5 (NOT necessarily elevated urinary uric acid)</td>
<td>Acidic urine, pH &lt;5.5 (NOT necessarily elevated urinary uric acid)</td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Medical if stone &lt;5 mm and no complications</td>
<td>Medical if stone &lt;5 mm and no complications</td>
<td>Complete stone clearance ABx for 6 wk</td>
<td>Invasive flushing results in increased fluid intake (3-4 L of urine/d)</td>
</tr>
<tr>
<td></td>
<td>Procedural/Surgical treatment if stone &gt;5 mm or presence of complications (see U17 for treatment)</td>
<td>Procedural/Surgical treatment if stone &gt;5 mm or presence of complications (see U17 for treatment)</td>
<td>Regular follow-up urine cultures</td>
<td>Alkalize urine (bicarbonate, potassium citrate), Penicillamine/α-MPG or Captopril (form complex with cystine)</td>
</tr>
<tr>
<td></td>
<td>Flows to increase urine volume to &gt;2 L/d</td>
<td>Flows to increase urine volume to &gt;2 L/d</td>
<td>Increased fluid intake ABx for 6 wk</td>
<td>ESWL not effective</td>
</tr>
<tr>
<td></td>
<td>For calcium stones: cellulose phosphate, orthophosphate for absorptive causes</td>
<td>For calcium stones: cellulose phosphate, orthophosphate for absorptive causes</td>
<td>Alkalization of urine to pH 6.5 to 7 (bicarbonate, potassium citrate) ± allopurinol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium oxalate: thioureas, ± potassium citrate, ± allopurinol</td>
<td>Calcium oxalate: thioureas, ± potassium citrate, ± allopurinol</td>
<td>Calcium struvite: ABx (stone must be removed) to treat infection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium struvite: ABx (stone must be removed) to treat infection</td>
<td>Calcium struvite: ABx (stone must be removed) to treat infection</td>
<td>Calcium struvite: ABx (stone must be removed) to treat infection</td>
<td></td>
</tr>
</tbody>
</table>

Note:
- E. coli positive urine dip and cultures if stone >10mm confirmed by imaging.
- Autosomal recessive defect in small bowel mucosal absorption and renal tubular absorption of dibasic amino acids results in “COLA” in urine (cystine, ornithine, lysine, arginine).
- Aggressive stone disease seen in children and young adults.
- Recurrent stone formation, family Hx.
- Often staghorn calculi.
- Faintly radiopaque on KUB.
- Positive urine sodium nitroprusside test, urine chromatography for cystine.

Purpose: To determine whether or not alpha blockers compared with other pharmacological treatments or placebo improve stone clearance rates and other clinically relevant outcomes in patients presenting with symptoms of stones less than 10 mm confirmed by imaging.

Results/Conclusions: 32,197 yrs, 5,964 participants. Although patients using alpha-blockers were more likely to experience adverse effects compared to standard therapy, stone-free rates were significantly higher in the alpha-blocker group (RR 1.49, 95% CI 1.33-1.64), expulsion time was 2.91 days shorter, and there was a reduction in the number of pain episodes (MD -0.48, 95% CI -0.94 to -0.01), the need for analgesic medication (MD -38.17, 95% CI -74.93 to -1.41), and hospitalization (RR 0.35, 95% CI 0.13-0.97). Alpha blockers should therefore be offered as a primary treatment modality for ureteral stones.
Urological Neoplasms

Approach to Renal Mass

Figure 9. Workup of a renal mass
*Imaging modality may be different in cases of contrast allergy or elevated creatinine

Benign Renal Neoplasms

CYSTIC KIDNEY DISEASE

- **simple cysts**: usually solitary or unilateral
  - very common: up to 50% at age 50
  - usually incidental finding on abdominal imaging
  - **Bosniak Classification** is used to stratify for risk of malignancy based on cyst features from contrast CT
- **polycystic kidney disease**
  - autosomal recessive: multiple bilateral cysts, often leading to early renal failure in infants
  - autosomal dominant: progressive bilateral disease leading to HTN and renal failure, adult-onset
- **medullary sponge kidney**: cystic dilatation of the collecting ducts
  - usually benign course, but patients are predisposed to stone disease
- **von Hippel-Lindau syndrome**: multiple bilateral cysts or clear cell carcinomas (50% incidence of RCC)
  - renal cysts, cerebellar, spinal and retinal hemangioblastomas, pancreatic and epididymal cysts, pheochromocytomas

Table 15. Bosniak Classification of Renal Cysts

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
<th>Features</th>
<th>Risk of Malignancy</th>
<th>Management Plan</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Simple cyst</td>
<td>Round, no septations, no calcifications, no solid component</td>
<td>Near zero</td>
<td>Follow-up usually not required</td>
</tr>
<tr>
<td>II</td>
<td>Simple cyst</td>
<td>A few thin septa, no true enhancement, well-marginated, uniform high attenuation, &lt;3 cm</td>
<td>Minimal</td>
<td>Follow-up usually not required</td>
</tr>
<tr>
<td>III</td>
<td>Minimally complex cyst with extra features that require follow-up</td>
<td>Still well-marginated and non-enhancing, but now multiple thin septa or some thickening/calcification of septa/wall, &gt;3 cm</td>
<td>5-20%</td>
<td>Requires follow-up with imaging q6-12mo If the lesion evolves, may require surgical resection</td>
</tr>
<tr>
<td>III</td>
<td>Complex cyst</td>
<td>Thicker or more irregular walls with measurable enhancement</td>
<td>&gt;50%</td>
<td>Requires surgical resection</td>
</tr>
<tr>
<td>IV</td>
<td>Clearly malignant</td>
<td>Class III + enhancing soft-tissue components</td>
<td>&gt;90%</td>
<td>Requires surgical resection</td>
</tr>
</tbody>
</table>
Table 16. Benign Renal Masses

<table>
<thead>
<tr>
<th>Angiomyolipoma (Renal Hamartoma)</th>
<th>Renal Oncocytoma</th>
<th>Renal Adenoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>&gt;1% of adult renal tumours</td>
<td>3-7% of renal tumours</td>
</tr>
<tr>
<td>Medicine</td>
<td>F&gt;M</td>
<td>M&gt;F</td>
</tr>
<tr>
<td>Age 20% associated with tuberous sclerosis (especially if multiple, recurrent)</td>
<td>Oncocytomas also found in adrenal, thyroid and parathyroid glands</td>
<td>Incidence increases with age</td>
</tr>
<tr>
<td>Found in 7-23% of all autopsies</td>
<td>Spherical, capsulated with possible central scar</td>
<td>Found in 7-23% of all autopsies</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Clonal neoplasm consisting of blood vessels (angio-), smooth muscle (-myo-), and fat (-lipoma) May extend into regional lymphatics and other organs and become symptomatic</td>
<td>Small cortical lesions &lt;1 cm Majority are solitary but can be multifocal</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Incidental finding on CT Negative attenuation (≤20 HU) on CT is pathognomonic Rare presentation of hematuria, flank pain, and palpable mass (same as RCC)</td>
<td>Incidental finding on CT Rarely symptomatic</td>
</tr>
<tr>
<td>Renal angiomyolipoma is almost always benign; the imaging features are unique</td>
<td>Incidental finding on CT Difficult to distinguish from RCC on imaging – treated as RCC until proven otherwise Biopsy may be performed to rule out malignancy</td>
<td>Incidental finding on CT Controversy as to whether this represents benign or pre-malignant neoplasm</td>
</tr>
<tr>
<td>Management</td>
<td>May consider surgical excision or embolization if symptomatic (pain, bleeding) or higher risk of bleeding (e.g. pregnancy) Potential role for mTOR inhibitors in unresectable/metastatic disease Follow with serial U/S</td>
<td>Partial/radical nephrectomy for large masses HIFU or RFA for smaller masses</td>
</tr>
</tbody>
</table>

Malignant Renal Neoplasms

RENAAL CELL CARCINOMA

Etiology
- cause unknown
- originates from proximal convoluted tubule epithelial cells in clear cell subtype (most common)
- hereditary forms seen with von Hippel-Lindau syndrome and hereditary papillary renal carcinoma

Epidemiology
- 8th most common malignancy (accounts for 3% of all newly diagnosed cancers)
- 85% of primary malignant tumours in kidney
- M:F = 3:2
- peak incidence at 50-60 yr of age

Pathology
- histological subtypes: clear cell (75-85%), papillary (10-15%), chromophobic (5-10%), collecting duct
- sarcomatoid elements in any subtype is a poor prognostic factor

Risk Factors
- top 3 risk factors: smoking, HTN, obesity
- miscellaneous: horseshoe kidney, acquired renal cystic disease
- role of environmental exposures (aromatic hydrocarbons, etc.) remains an unproven risk factor for development of RCC

Clinical Features
- usually asymptomatic: frequently diagnosed incidentally by U/S or CT
- poor prognostic indicators: weight loss, weakness, anemia, bone pain
- classic “too late triad” found in 10-15%
  - gross hematuria 50%
  - flank pain <50%
  - palpable mass <30%
- was called the “internist’s tumour” because of paraneoplastic symptomatology – now called the “radiologist’s tumour” because of incidental diagnosis via imaging
- metastases: seen in 1/3rd of new cases; additional 20-40% will go on to develop metastases
  - bone, brain, lung and liver most common site
  - may invade renal veins and inferior vena cava lumen. This may result in ascites, hepatic dysfunction, right atrial tumour, and pulmonary emboli

Investigations
- routine labs for paraneoplastic syndromes (CBC, ESR, LFTs, extended electrolytes)
- U/A (60-75% have hematuria)
- renal U/S: solid vs. cystic lesion

RCC Systemic Effects: paraneoplastic syndromes (10-40% of patients)
- Hematopoietic disturbances: anemia, polycythemia, raised ESR
- Endocrinopathies: hypercalcemia (increased vitamin D hydroxylation), erythrocytosis (increased erythropoietin), HTN (increased renin), production of other hormones (prolactin, gonadotropins, TSH, insulin, and cortisol)
- Hepatic cell dysfunction or Stauffer syndrome: abnormal LFTs, decreased WBC count, fever, areas of hepatic necrosis; no evidence of metastases; reversible following removal of primary tumour
- Hemodynamic alterations: systolic HTN (due to AV shunting), peripheral edema (due to caval obstruction)
• contrast-enhanced CT: higher sensitivity than U/S for detection of renal masses and for staging purposes
• MRI: useful for evaluation of vascular extension
• renal biopsy: to confirm diagnosis if considering observation or other non-surgical therapy

Staging
• involves CT, CXR, liver enzymes and LFTs, bone/head imaging (if symptoms dictate)

Table 17. 2010 TNM Classification of Renal Cell Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1: tumour &lt; 7 cm, confined to renal parenchyma</td>
<td>N0: no regional nodes</td>
<td>M0: no evidence of metastasis</td>
</tr>
<tr>
<td>T1a: &lt; 4 cm</td>
<td>N1: metastasis to a single node, &lt; 2 cm</td>
<td></td>
</tr>
<tr>
<td>T1b: 4 - 7 cm</td>
<td>N2: metastasis to a single node between 2 - 5 cm or multiple nodes &lt; 2 cm</td>
<td></td>
</tr>
<tr>
<td>T2: tumour &gt; 7 cm, confined to renal parenchyma</td>
<td>N3: node &gt; 5 cm</td>
<td></td>
</tr>
<tr>
<td>T2a: tumour &gt; 7 cm but ≤ 10 cm in greatest dimension, limited to the kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2b: tumour &gt; 10 cm, limited to the kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3: tumour extends into major veins or perinephric tissues, but NOT into ipsilateral adrenal or beyond Gerota’s fascia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3a: into renal vein or sinus fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3b: into infradiaphragmatic IVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3c: into supradiaphragmatic IVC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4: tumour extends beyond Gerota’s fascia including extension into ipsilateral adrenal</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Treatment
• surgical
  • radical nephrectomy: en bloc removal of kidney, tumour, ipsilateral adrenal gland (in upper pole tumours) and intact Gerota’s capsule and paraaortic lymphadenectomy
  • partial nephrectomy (parenchyma-sparing): small tumour (roughly <4 cm) or solitary kidney/bilateral tumours
  • surgical removal of solitary metastasis may be considered
  • ablative techniques (cryoablation, RFA)
  • palliative radiation to painful bony lesions
  • therapy for advanced stage
    • tyrosine kinase inhibitors for metastatic disease (e.g. sunitinib, sorafenib)
    • anti-angiogenesis/anti-VEGF (e.g. bevacizumab)
    • mTOR inhibitors (e.g. temsirolimus, everolimus)
    • high-dose IL-2 (high toxicity but able to induce long-term cure in 5-7% of patients)
    • IFN α: monotherapy has been largely replaced by molecularly targeted agents listed above

Prognosis
• stage at diagnosis most important prognostic factor
  • T1: 90-100% 5 yr survival
  • T2-T3: 60% 5 yr survival
  • metastatic disease: <5% 10 yr survival

Carcinoma of the Renal Pelvis and Ureter

Etiology
• risk factors include
  • smoking
  • chemicals/dietary exposures (industrial dyes and solvents; aristolochic acid)
  • analgesic abuse (acetaminophen, ASA, and phenacetin)
  • Balkan nephropathy

Epidemiology
• rare: accounts for 5% of all urothelial cancers
• frequently multifocal, 2-5% are bilateral
• M:F = 3:1
• relative incidence: bladder:renal:ureter = 100:1:1

Pathology
• 85% are papillary urothelial cell carcinoma; others include SCC and adenocarcinoma
• UCC of ureter and renal pelvis are histologically similar to bladder UCC

Clinical Features
• gross/microscopic hematuria
• flank pain
• storage or voiding symptoms (dysuria only if lower urinary tract involved)
• flank mass ± hydronephrosis (10-20%)
Investigations
- IVP/CT urogram
- cystoscopy and retrograde pyelogram

Treatment
- radical nephroureterectomy with cuff of bladder
- distal ureterectomy for distal ureteral tumours
- emerging role for endoscopic laser ablation in patients with low grade disease, poor baseline renal health

Bladder Carcinoma

Etiology
- unknown, but environmental risk factors include
  - smoking (main factor – implicated in 60% of new cases)
  - aromatic amines: naphthylamines, benzidine, tryptophan, phenacetin metabolites
  - cyclophosphamide
  - prior Hx of radiation treatment to the pelvis
  - Schistosoma hematobium infection (associated with SCC)
  - chronic irritation: cystitis, chronic catheterization, bladder stones (associated with SCC)
  - aristolochic acid: associated with Balkan Nephropathy (renal failure, upper tract urothelial cancer) and Chinese Herbal Nephropathy

Epidemiology
- 2nd most common urological malignancy
- M:F = 3:1, more common among whites than blacks
- mean age at diagnosis is 65 yr

Pathology
- classification
  - UCC >90%
  - SCC 5-7%
  - adenosquamous carcinoma 1%
  - others <1%
- stages and prognoses of urothelial carcinoma at diagnosis
  - non-muscle invasive (75%) ➔ >80% overall survival
    - 15% of these will progress to invasive UCC
  - the majority of these patients will have recurrence
  - invasive (25%) ➔ 50-60% 5 yr survival
    - 85% have no prior Hx of superficial UCC (i.e. de novo)
    - 50% have occult metastases at diagnosis, and most of these will develop overt clinical evidence of metastases within 1 yr – lymph nodes, lung, peritoneum, liver
- carcinoma in situ ➔ flat, non-papillary erythematous lesion characterized by dysplasia confined to urothelium
  - more aggressive, worse prognosis
  - usually multifocal
  - may progress to invasive UCC

Clinical Features
- asymptomatic (20%)
- hematuria (key symptom: 85-90% at the time of diagnosis)
- pain (50%) ➔ location determined by size/extent of tumour (i.e. flank, suprapubic, perineal, abdominal, etc.)
- clot retention (17%)
- storage urinary symptoms ➔ consider carcinoma in situ
- palpable mass on bimanual exam ➔ likely muscle invasion
- obstruction of ureters ➔ hydronephrosis and uremia (nausea, vomiting, and diarrhea)

Investigations
- U/A, urine C&S, urine cytology
- U/S
- CT scan with contrast ➔ look for filling defect
- cystoscopy with biopsy (gold standard)
- biopsy to establish diagnosis and to determine depth of penetration
- specific bladder tumour markers (e.g. NMP-22, BTA, Immunocyt, FDP)

Grading
- low grade: <=10% invasive, 60% recur
- high grade: 50-80% are invasive or should progress to invasive over time

Staging
- for invasive disease: CT or MRI, CXR, LFTs, extended electrolytes (Ca²⁺, Mg²⁺, PO₄³⁻) (metastatic workup)
### Table 18. 2010 TNM Classification of Bladder Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TX</td>
<td>Primary tumour cannot be assessed</td>
<td>M0: No distant metastasis</td>
</tr>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
<td>N0: No lymph node metastasis</td>
</tr>
<tr>
<td>Tis</td>
<td>Carcinoma in situ: &quot;flat tumour&quot;</td>
<td>N1: Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour invades subepithelial connective tissue</td>
<td>N2: Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)</td>
</tr>
<tr>
<td>T2a</td>
<td>Tumour invades superficial muscularis propria (inner half)</td>
<td>N3: Lymph node metastasis to the common iliac lymph nodes</td>
</tr>
<tr>
<td>T2b</td>
<td>Tumour invades deep muscularis propria (outer half)</td>
<td></td>
</tr>
<tr>
<td>T3</td>
<td>Tumour invades perivesical tissue</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>Tumour invades prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall</td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>Tumour invades pelvic wall, abdominal wall</td>
<td></td>
</tr>
</tbody>
</table>

### Figure 11. Urothelial carcinoma of bladder

**Treatment**
- superficial (non-muscle invasive) disease: Tis, Ta, T1
  - low-grade disease
  - single dose mitomycin c within 24 hours of resection reduces recurrence rates
  - TURBT ± intravesical chemo/immuno-therapy (e.g. BCG, mitomycin C) to decrease recurrence rate
  - maintenance with intravesical chemotherapy with BCG for 3 cycles every 3 mo, may be continued for 2-3 yr
- invasive disease: T2a, T2b, T3
  - radical cystectomy + pelvic lymphadenectomy with urinary diversion (e.g. ileal conduit, Indiana pouch, ileal neobladder) or TURBT + chemo-radiation (bladder sparing) for small tumours with non-obstructed ureters
  - neo-adjuvant chemotherapy prior to cystectomy may also be done
  - use of adjuvant chemotherapy after definitive local treatment is controversial
- advanced/metastatic disease: T4a, T4b, N+, M+
  - initial combination of systemic chemotherapy ± irradiation ± surgery

### Prognosis
- depends on stage, grade, size, number of lesions, recurrence and presence of CIS
  - T1: 90% 5 yr survival
  - T2: 55% 5 yr survival
  - T3: 20% 5 yr survival
  - T4/N+/M+: <5% 5 yr survival

**Prostate Cancer**

### Etiology
- not known
- risk factors
  - increased incidence in persons of African descent
  - high dietary fat = 2x risk

**Figure 12. Ileal conduit, Indiana pouch, ileal neobladder**

### Neoadjuvant Chemotherapy plus Cystectomy Compared with Cystectomy Alone for Locally Advanced Bladder Cancer

**NEJM 2003;349:859-866**

**Study:** Randomized clinical trial.
**Patients:** 317 patients with transitional-cell carcinoma of the bladder (T2NM0 to T4aN0M0).
**Intervention:** Randomized to undergo radical cystectomy or to receive three cycles of combined chemotherapy (methotrexate, vinblastine, doxorubicin, and cisplatin) followed by radical cystectomy.
**Main Outcome:** Survival. Secondary objective was to quantify down-staging of tumour following chemotherapy.
**Results:** At 5 yr after treatment initiation, 57% of the combination-therapy group vs. 43% of the cystectomy group were alive (p = 0.06). In the combination-therapy group, 38% of the patients were pathologically free of cancer at the time of cystectomy vs. 15% of the cystectomy-only group at the time of surgery (p < 0.001).
**Conclusions:** For locally advanced bladder carcinoma, neoadjuvant chemotherapy significantly reduces tumour volume and also improves survival.
• family Hx
  • 1st degree relative = 2x risk
  • 1st and 2nd degree relatives = 9x risk

Epidemiology
• most prevalent cancer in males
• 3rd leading cause of male cancer deaths (following lung and colon)
• up to 50% risk of CaP at age 50
• lifetime risk of death from CaP is 3%
• 75% diagnosed between ages of 60 and 85; mean age at diagnosis is 72

Pathology
• adenocarcinoma
  • >95%, often multifocal
• urothelial carcinoma of the prostate (4.5%)
  • associated with UCC of bladder; does NOT follow TNM staging below; not hormone-responsive
• endometrial (rare)
  • carcinoma of the utricle

Anatomy (see Figure 7, U7)
• 60-70% of nodules arise in the peripheral zone
• 10-20% arise in the transition zone
• 5-10% arise in the central zone

Clinical Features
• usually asymptomatic
• most commonly detected by DRE, elevated PSA, or as an incidental finding on TURP
  • DRE: hard irregular nodule or diffuse dense induration involving one or both lobes
  • PSA: see Prostate Cancer Screening, U26
• locally advanced disease
  • storage and voiding symptoms, ED (all uncommon without spread)
• metastatic disease
  • bony metastases to axial skeleton common
  • visceral metastases are less common (liver, lung, and adrenal gland most common sites)
  • leg pain and edema with nodal metastases obstructing lymphatic and venous drainage

Methods of Spread
• local invasion
• lymphatic spread to regional nodes
  • obturator > iliac > presacral/para-aortic
• hematogenous dissemination occurs early

Investigations
• DRE
• PSA elevated in the majority of patients with CaP
• TRUS-guided needle biopsy
• bone scan may be omitted in untreated CaP with PSA <10 ng/mL
• CT scanning to assess metastases
• MRI: being investigated for possible role in detection, staging, MRI-guided biopsying and active surveillance

Table 19. 2010 TNM Classification of Prostate Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1: clinically undetectable tumour, normal DRE and TRUS</td>
<td>N0: no regional lymph node metastasis</td>
<td>M0: no distant metastasis</td>
</tr>
<tr>
<td>T1a: tumour incidental histologic finding in &lt;5% of tissue resected</td>
<td>NX: regional lymph nodes were not assessed</td>
<td>M1: distant metastasis</td>
</tr>
<tr>
<td>T1b: tumour incidental histologic finding in &gt;5% of tissue resected</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1a: nonregional lymph nodes</td>
</tr>
<tr>
<td>T1c: tumour identified by needle biopsy (due to elevated PSA level)</td>
<td>N0: no regional lymph node metastasis</td>
<td>M1b: bone(s)</td>
</tr>
<tr>
<td>T2: palpable, confined to prostate</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T2a: tumour involving &lt; one half of one lobe</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T2b: tumour involving &gt; one half of one lobe, but not both lobes</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T2c: tumour involving both lobes</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T3: tumour extends through prostate capsule</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T3a: extracapsular extension (unilateral or bilateral)</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T3b: tumour invading seminal vesicle(s)</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
<tr>
<td>T4: tumour invades adjacent structures (besides seminal vesicles)</td>
<td>N1: spread to regional lymph nodes</td>
<td>M1c: other site(s) with or without bone disease</td>
</tr>
</tbody>
</table>
Table 20. Prostate Cancer Mortality Risk

<table>
<thead>
<tr>
<th>Low Risk</th>
<th>Intermediate Risk (if any of following)</th>
<th>High Risk (if any of following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSA</td>
<td>&lt;10</td>
<td>10-20</td>
</tr>
<tr>
<td>Gleason Score</td>
<td>&lt;7</td>
<td>7</td>
</tr>
<tr>
<td>Stage</td>
<td>pT1-2a</td>
<td>pT2b-pT2c</td>
</tr>
</tbody>
</table>

Treatment
- T1/T2 (localized, low-risk)
  - if adequate life expectancy or no other significant comorbidities, consider active surveillance vs. definitive local treatment (RP, brachytherapy, or EBRT)
  - no difference in cure rate between definitive treatment modalities
- in older population: watchful waiting + palliative treatment for symptomatic progression
- T1/T2 (intermediate or high-risk)
  - definitive therapy over active surveillance
- T3, T4
  - EBRT + androgen deprivation therapy or RP + adjuvant EBRT
- N >0 or M >0
  - requires hormonal therapy/palliative radiotherapy for metastases; may consider combined androgen blockade
  - bilateral orchectomy – removes 90% of testosterone
  - GnRH agonists (e.g. leuprolide, goserelin)
  - GnRH antagonist (e.g. degarelix)
  - estrogens (e.g. diethylstilbestrol [DES])
  - antiandrogens (e.g. bicalutamide)
  - local irradiation of painful secondary or half-body irradiation
- hormone-refractory prostate cancer
  - chemotherapy: docetaxel, cabazitaxel, sipuleucel-T

Table 21. Treatment Options for Localized Prostate Cancer

<table>
<thead>
<tr>
<th>Modality</th>
<th>Population Considered</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watchful Waiting</td>
<td>Short life expectancy (&lt;5-10 yr); will likely only receive non-curative hormonal therapy if disease progresses</td>
<td>Disease progression</td>
</tr>
<tr>
<td>Active Surveillance (serial PSA, DRE, and biopsies)</td>
<td>Low grade disease, good follow-up; is still considering more curative treatment if disease progresses</td>
<td>Disease progression; decrease in QOL associated with serial testing; risks associated with biopsies; no optimal monitoring schedule has been defined to date</td>
</tr>
<tr>
<td>Brachytherapy</td>
<td>Low volume, low PSA (&lt;10), low grade</td>
<td>Radiation proctitis (5%), ED (50%), risk of rectal cancer</td>
</tr>
<tr>
<td>EBRT</td>
<td>Locally advanced disease, older patients</td>
<td>Radiation proctitis (5%), ED (50%), risk of rectal cancer</td>
</tr>
<tr>
<td>RP</td>
<td>Young patients (&lt;75 yr), high-risk disease</td>
<td>Incontinence (10%), ED (30-50%)</td>
</tr>
</tbody>
</table>

*Other options include cryoablation, HIFU, hormonal ablation

Prognosis
- T1-T2: comparable to normal life expectancy
- T3-T4: 40-70% 10-yr survival
- N+ and/or M+: 4 % 5 yr survival
- prognostic factors: tumour stage, tumour grade, PSA value, PSA doubling time

Prostate Cancer Screening

Digital Rectal Exam
- should be included as part of initial screening
- suspicious findings: abnormal feeling, nodularity, focal lesion, discrete change in texture/fullness/symmetry

Prostate Specific Antigen
- glycoprotein produced by epithelial cells of prostate gland
- leaks into circulation in setting of disrupted glandular architecture
- value of <4 ng/mL traditionally considered as cut-off to differentiate normal from pathologic value, but no single justifiable cutpoint
- measured serum PSA is a combination of free (15%) and bound PSA (85%)
- PSA velocity, PSA density, and free:total PSA: all intended to increase sensitivity and specificity of serum PSA values
  - association of increased CaP rates with decreased free are total PSA, elevated PSA velocity and density

Screening Recommendations
- conflicting evidence regarding mortality reduction with PSA-based screening and debate regarding overdiagnosis/oftreatment

Radical Prostatectomy vs. Watchful Waiting in Early Prostate Cancer (Scandinavian Prostate Cancer Group Study)
- Methods: 731 men at 52 United States centres with localized prostate cancer participated.
- Results: For men with low-risk prostate cancer (PSA<10, Gleason score<7), at 15 yr after treatment initiation, the relative risk of death due to prostate cancer in the radical prostatectomy group versus watchful waiting was 0.62 (p=0.01). The cumulative incidence of death from prostate cancer after radical prostatectomy was as compared with other studies.
- Conclusions: Radical prostatectomy was associated with increased rate of death due to prostate cancer.

Radical Prostatectomy vs. Observation for Localized Prostate Cancer (Prostate Cancer Intervention vs. Observation Trial [PIVOT] Study Group)
- Methods: 731 men at 52 United States centres with localized prostate cancer participated.
- Results: Radical prostatectomy did not reduce all-cause or prostate cancer mortality relative to observation (relative risk 0.80, p=0.09), through at least 12 yr of follow-up.
- Conclusions: Observation is recommended for localized prostate cancer, especially in men with low PSA and low-risk disease.

Causes of Increased PSA
- BPH, prostatectasis, prostatic ischemia/infarction, prostate biopsy/surgery, prostatic massage, acute urinary retention, urethral catheterization, cystoscopy, TRUS, strenuous exercise, perineal trauma, ejaculation, acute renal failure, coronary bypass graft, radiation therapy

PSA is specific to the PROSTATE, but NOT to prostate cancer
**Canadian Urological Association Guidelines (2011) re: CaP Screening**

- harms and benefits of PSA testing must be explained to the patient and an informed, shared decision to test must be established
- initial screening should include both serum PSA and DRE
- all men should be offered screening at age 50 if >10 yr life-expectancy
- high-risk individuals (family Hx of CaP or African ancestry) should be offered screening at age 40 if >10 yr life-expectancy
- standard has been annual screening, but q2-4yr screening acceptable
- no strict cutoff for when to biopsy. Decision to biopsy should be based on more than a single PSA value

*new guidelines under development, however, AUA guidelines recommend against universal routine PSA screening for CaP*
Staging
- Clinical: CXR (lung mets), markers for staging (β-hCG, AFP, LDH), CT abdomen/pelvis (retroperitoneal lymphadenopathy)
  - Stage I: disease limited to testis, epididymis, or spermatic cord
  - Stage II: disease limited to the retroperitoneal nodes
  - Stage III: disease metastatic to supradiaphragmatic nodal or visceral sites

Table 22. 2010 TNM Classification of Testicular Carcinoma

<table>
<thead>
<tr>
<th>T</th>
<th>N</th>
<th>M</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ti:</td>
<td>intratubular germ cell neoplasia</td>
<td>N status: same as RCC</td>
</tr>
<tr>
<td>T1:</td>
<td>limited to testis and epididymis without vascular/lymphatic invasion</td>
<td>M0: no distant mets</td>
</tr>
<tr>
<td>T2:</td>
<td>limited to testis and epididymis with vascular/lymphatic invasion</td>
<td>M1: distant mets</td>
</tr>
<tr>
<td>T3:</td>
<td>invasion of the spermatic cord ± vascular/lymphatics</td>
<td>M1a: nonregional lymph node(s) or pulmonary mets</td>
</tr>
<tr>
<td>T4:</td>
<td>invasion of the scrotum ± vascular/lymphatics</td>
<td>M1b: distant mets other than to regional lymph nodes and lung</td>
</tr>
</tbody>
</table>

Management
- orchiectomy through inguinal ligament for all stages
- consider sperm banking, testicular prosthesis
- adjuvant therapies

Prognosis
- 99% cured with stage I and II disease
- 70-80% complete remission with advanced disease

Penile Tumours

Epidemiology
- rare (<1% of cancer in males in U.S.)
- most common in 6th decade

Benign
- cyst, hemangioma, nevus, papilloma

Pre-Malignant
- balanitis xerotica obliterans, leukoplaikia, Buschke-Lowenstein tumour (large condyloma)

Pre-invasive Cancer
- carcinoma in situ
  - Bowen's disease → crusted, red plaques on the shaft
  - erythroplasia of Queyrat → velvet red, ulcerated plaques on the glans
  - treatment options: local excision, laser, radiation, topical 5-fluorouracil

Malignant
- risk factors
  - chronic inflammatory disease
  - STI
  - phimosis
  - uncircumcised penis
  - 2% of all urogenital cancers
  - SCC (>95%), basal cell, melanoma, Paget's disease of the penis (extremely rare)
  - definitive diagnosis requires full thickness biopsy of lesion
  - lymphatic spread (superficial/deep inguinal nodes → iliac nodes) >> hematogenous
Treatment
- wide surgical excision with tumour-free margins (dependent on extent and area of penile involvement) ± lymphadenectomy
- consider less aggressive treatment modalities in CIS (cryotherapy, laser therapy, etc.) if available

### Scrotal Mass

#### Table 23. Differentiating between Scrotal Masses

<table>
<thead>
<tr>
<th>Condition</th>
<th>Pain</th>
<th>Palpation</th>
<th>Additional Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torsion</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>Absent cremaster reflex, negative Prehr’s sign</td>
</tr>
<tr>
<td>Epididymitis (U16)</td>
<td>+</td>
<td>Epididymal tenderness</td>
<td>Present cremaster reflex, positive Prehr’s sign</td>
</tr>
<tr>
<td>Orchitis (U16)</td>
<td>+</td>
<td>Diffuse tenderness</td>
<td>Present cremaster reflex, positive Prehr’s sign</td>
</tr>
<tr>
<td>Hematocele</td>
<td>–</td>
<td>Testis not separable from hydrocele, cord palpable</td>
<td>Transillumination, Hx of trauma</td>
</tr>
<tr>
<td>Hydrocele</td>
<td>–</td>
<td>Testis separable from spermatocele, cord palpable</td>
<td>Transillumination</td>
</tr>
<tr>
<td>Spermatocele</td>
<td>–</td>
<td>Bag of worms</td>
<td>No transillumination, increases in size with Valsalva, decrease in size if supine</td>
</tr>
<tr>
<td>Indirect Inguinal</td>
<td>– (± if strangulated)</td>
<td>Hard lump/nodule</td>
<td>No transillumination</td>
</tr>
<tr>
<td>Tumour</td>
<td>– (± if hemorrhagic)</td>
<td>Diffuse swelling</td>
<td>Often post-operative or immobilized, check for liver dysfunction</td>
</tr>
<tr>
<td>Generalized/Dependant edema</td>
<td>–</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Idiopathic</td>
<td>–</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Table 24. Benign Scrotal Masses

<table>
<thead>
<tr>
<th>Type</th>
<th>Varicocele</th>
<th>Spermatocele</th>
<th>Hydrocele</th>
<th>Testicular Torsion</th>
<th>Inguinal Hernia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Dilatation and tortuosity of pampiniform plexus</td>
<td>A benign, sperm filled epididymal retention cyst</td>
<td>Collection of serous fluid that results from a defect or irritation in the tunica vaginalis</td>
<td>Twisting of the testicle causing venous occlusion and engorgement as well as arterial ischemia and infarction</td>
<td>Protrusion of abdominal contents through the inguinal canal into the scrotum</td>
</tr>
<tr>
<td>Etiology</td>
<td>15% of men Due to incompetent valves in the testicular veins 90% left sided</td>
<td>Multiple theories, including: Distal obstruction Aneurysmal dilations of the epididymis Agglutinated germ cells</td>
<td>Usually idiopathic Found in 5-10% testicular tumours Associated with trauma/infection Communicating: patent processus vaginalis, changes size during day (peds) Non-communicating: non-patient processus vaginalis (adult)</td>
<td>Trauma Cryptorchidism “Bell clapper deformity” Many occur in sleep (50%) Necrosis of glands in 5-6 h</td>
<td>Indirect (through internal ring, often into scrotum): congenital Direct (through external ring, rarely into scrotum): abdominal muscle weakness</td>
</tr>
<tr>
<td>Hx/P/E</td>
<td>“Bag of worms” Often painless Pulsates with Valsalva</td>
<td>Non-tender, cystic mass Transilluminates</td>
<td>Non-tender, intrascrotal mass Cystic Transilluminates</td>
<td>Acute onset severe scrotal pain, swelling GI upsets cases Retracted and transverse testicle (horizontal lie) Negative Prehr’s sign Absent cremasteric reflex</td>
<td>A small bulge in the groin that may increase in size with Valsalva and disappear when lying down Can present as a swollen or enlarged scrotum Discomfort or sharp pain – especially when straining, lifting, or exercising</td>
</tr>
<tr>
<td>Investigations</td>
<td>P/E Valsava</td>
<td>P/E U/S to rule out tumour</td>
<td>U/S to rule out tumour</td>
<td>U/S with colour flow Doppler probe over testicular artery Decrease uptake on 99mTc-pertechnetate scintillation scan (doughnut sign)</td>
<td>Hx and P/E Invagination of the scrotum Valsalva</td>
</tr>
<tr>
<td>Treatment</td>
<td>Conservative Surgical ligation of testicular veins Percutaneous vein occlusion (balloon, sclerosing agents) Repair may improve sperm count/motility 50-75%</td>
<td>Conservative Avoid needle aspiration as it can lead to infection, reaccumulation and spilling of irritating sperm within scrotum Excise if symptomatic</td>
<td>Conservative Needle drainage Surgical</td>
<td>Emergency surgical exploration and bilateral orchiopexy Orchiectomy if poor prognosis</td>
<td>Surgical repair</td>
</tr>
</tbody>
</table>

### Varicocele Grading
- Grade 1: Palpable only with Valsalva manoeuvre
- Grade 2: Palpable without Valsalva
- Grade 3: Visible through scrotal skin

Suspect a Retroperitoneal Mass/Process in a Patient with a Varicocele if
- Acute onset
- Right sided (isolated)
- Palpable abdominal mass
- Does not reduce while supine

Indications for Treatment of Varicocele
- Impaired sperm quality or quantity
- Pain or dull ache affecting QOL
- Affected testis fails to grow in adolescents
- Cosmetic indications (especially in adolescents)
TORSION OF TESTICULAR APPENDIX

- twisting of testicular/epididymal vestigial appendix

Signs and Symptoms

- clinically similar to testicular torsion, but vertical lie and cremaster reflex preserved
- “blue dot sign”
  - blue infarcted appendage seen through scrotal skin (can usually be palpated as small, tender lump)

Treatment

- analgesia – most will subside over 5-7 d
- surgical exploration and excision if refractory pain

HEMATOCELE

- trauma with bleed into tunica vaginalis
- U/S helpful to exclude fracture of testis which requires surgical repair

Treatment

- ice packs, analgesics, surgical repair

Differential of a Benign Scrotal Mass

His Bits

- Hydrocele
- Infection (epididymitis/orchitis)
- Sperm (spermatocele)
- Blood (hematocele)
- Intestines (hernia)
- Torsion
- Some veins (varicocele)

Penile Complaints

<table>
<thead>
<tr>
<th>Type</th>
<th>Peyronie’s Disease</th>
<th>Priapism</th>
<th>Paraphimosis</th>
<th>Phimosis</th>
<th>Premature Ejaculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Definition</td>
<td>Benign curvature of penile shaft secondary to fibrous thickening of tunica albuginea</td>
<td>Prolonged erection lasting &gt;4 h in the absence of sexual excitement/desire</td>
<td>Foreskin caught behind glans leading to edema → inability to reduce foreskin</td>
<td>Inability to retract foreskin over glans penis</td>
<td>Ejaculation prior to when one or both partners desire it, either before or soon after penetration</td>
</tr>
<tr>
<td>Etiology</td>
<td>Etiology unknown</td>
<td>50% idiopathic ischemic (common)</td>
<td>Iatrogenic (post cleaning/instrumentation)</td>
<td>Congenital (90% natural separation by age 3)</td>
<td>Psychological factors</td>
</tr>
<tr>
<td></td>
<td>Trauma/repeated inflammation</td>
<td>Ischemic (sickle cell)</td>
<td>Trauma</td>
<td>Balanitis</td>
<td>Primary: no period of acceptable control</td>
</tr>
<tr>
<td></td>
<td>Familial predisposition</td>
<td>Non-ischemic</td>
<td>Medications</td>
<td>Poor Hygiene</td>
<td>Secondary: symptoms after a period of control, not associated with general medical condition</td>
</tr>
<tr>
<td></td>
<td>Associated with DM, vascular disease, autoimmunity, Dupuytren’s contracture, erectile dysfunction</td>
<td>Neurogenic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hx/P/E</td>
<td>Penile curvature/shortening</td>
<td>Pain with erection</td>
<td>Painful erection ± signs of necrosis</td>
<td>Painful, swollen glans penis, foreskin</td>
<td>Limitation and pain when attempting to retract foreskin</td>
</tr>
<tr>
<td></td>
<td>Pain with erection</td>
<td>Poor erection distal to plaque</td>
<td></td>
<td>Constricting band proximal to corona</td>
<td>Balanoposthitis (infection of prepuce)</td>
</tr>
<tr>
<td>Investigations</td>
<td>Hx and P/E</td>
<td>Hx and P/E</td>
<td>Hx and P/E</td>
<td>Hx and P/E</td>
<td>Testosterone levels if in conjunction with impotence</td>
</tr>
<tr>
<td></td>
<td>Cavernosal blood gas analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment</td>
<td>Watchful waiting (spontaneous resolution in up to 50%)</td>
<td>Treat reversible causes</td>
<td>Manual pressure (with analgesia)</td>
<td>Proper hygiene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Intravasal or topical verapamil</td>
<td>High-flow:</td>
<td>Dorsal slit</td>
<td>Topical corticosteroids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Incision/excision of plaque</td>
<td>Self-limited</td>
<td>Circumcision (urgent or electively to prevent recurrence)</td>
<td>Dorsal slit</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shortening of less affected side ± penile prosthesis</td>
<td>Consider arterial embolization</td>
<td></td>
<td>Circumcision</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low-flow: Needle aspirated decompression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Phenylephrine intracorporal injection q3-5min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Surgical shunt no response within 1 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Erectile Dysfunction

Definition

- consistent (>3 mo duration) or recurrent inability to obtain or maintain an adequate erection for satisfactory sexual performance

Physiology

- erection involves the coordination of psychologic, neurologic, hemodynamic, mechanical, and endocrine components
- nerves: sympathetic (T11-L2), parasympathetic (S2-4), somatic (dorsal penile/pudendal nerves [S2-4])
• erection ("POINT")
  - parasympathetics → release of nitric oxide (NO) → increased cGMP levels within corpora cavernosa leading to:
    1. arteriolar dilatation
    2. sinusoidal smooth muscle relaxation → increased arterial inflow and compression of penile venous drainage (decreased venous outflow)
• emission ("SHOOT")
  - sensory afferents from glans
  - secretions from prostate, seminal vesicles, and ejaculatory ducts enter prostatic urethra (sympathetics)
• ejaculation ("SHOOT")
  - bladder neck closure (sympathetic)
  - spasmodic contraction of bulbo-cavernosus and pelvic floor musculature (somatic)
• detumescence
  - sympathetic nerves, norepinephrine, endothelin-1 → arteriolar and sinusoidal constriction → penile flaccidity

Classification

<table>
<thead>
<tr>
<th>Psychogenic</th>
<th>Organic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion</td>
<td>10%</td>
</tr>
<tr>
<td>Onset</td>
<td>Sudden</td>
</tr>
<tr>
<td>Frequency</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Variation</td>
<td>With partner and circumstance</td>
</tr>
<tr>
<td>Age</td>
<td>Younger</td>
</tr>
<tr>
<td>Organic Risk Factors</td>
<td>No organic risk factors</td>
</tr>
<tr>
<td>(HTN, DM, dyslipidemia)</td>
<td></td>
</tr>
<tr>
<td>Nocturnal/AM Erection</td>
<td>Present</td>
</tr>
</tbody>
</table>

Etiology ("IMPOTENCE")
• Iatrogenic: pelvic surgery, pelvic radiation
• Mechanical: Peyronie’s, priapism
• Psychological: depression, stress, anxiety, PTSD, widower syndrome
• Occlusive vascular: arterial HTN, DM, smoking, hyperlipidemia, PVD, venous (impaired veno-occlusion)
• Trauma: penile/pelvic, bicycling
• Extra factors: renal failure, cirrhosis, COPD, sleep apnea, malnutrition
• Neurogenic: CNS (e.g. Parkinson’s, MS, spinal cord injury, Guillain-Barré, spina bifida, stroke), PNS (e.g. DM, peripheral neuropathy)
• Chemical: antihypertensives, sedatives, antidepressants, antipsychotics, anxiolytics, antibiotics, antiandrogens (including 5-α reductase inhibitors), statins, GnRH agonists, illicit drugs
• Endocrine: DM, hypogonadism, hyperprolactinemia, hypo/ hyperthyroid

Diagnosis
• complete Hx (include sexual, medical, and psychosocial aspects)
• self-administered questionnaires (e.g. International Index of Erectile Function, Sexual Health Inventory for Men Questionnaire, ED Intensity Scale, ED Impact Scale)
• focused P/E, including vascular and neurologic examinations, secondary sexual characteristics
• lab investigations, dependent on clinical picture
  - risk factor evaluation: fasting blood glucose or HbA1c, cholesterol profile
  - optional: TSH, CBC, U/A, testosterone (free and total), prolactin, LH
• specialized testing including nocturnal penile tumescence monitoring usually unnecessary
• psychological/psychiatric assessment could be considered to rule out performance anxiety
• evaluation of penile vasculature only relevant with past history of trauma (i.e. pelvic fracture)

Treatment
• can often be managed by family doctor, see sidebar for when to refer
• must fully inform patient/partner of options, benefits and complications
• non-invasive
  - lifestyle changes (alcohol, smoking), psychological (sexual counseling and education)
  - change precipitating medications
  - treat underlying causes (DM, CVD, HTN, endocrinopathies)
• minimally invasive
  - oral medication (see Common Medications, U43)
    - sildenafil, tadalafil, vardenafil, avanafil: inhibits PDE-5 to increase intracavernosal cyclic GMP levels
      - all four have similar effectiveness, but tadalafil has certain advantages: earlier onset, longer half-life, no cyanopsia, can be taken on empty or full stomach (others better on empty stomach)
    - vacuum devices: draw blood into penis via negative pressure, then put ring at base of penis once erect
    - MUSE: male urethral suppository for erection – vasoactive substance (PGE1) capsule inserted into urethra
  - invasive
    - intracavernous vasodilator injection/self-injection
      - triple therapy (papaverine, phentolamine, PGE1) or PGE1 alone
      - complications: priapism (overdose), thickening of tunica albuginea at site of repeated injections (Peyronie’s plaque) and hematoma
  - surgical
    - penile implant (last resort): malleable or inflatable
    - penile artery reconstruction (in young men with isolated vascular lesion – investigational)

Trauma

• see Emergency Medicine, ER41

Renal Trauma

Classification According to Severity
• minor
  - contusions and superficial lacerations/hematomas: 90% of all blunt traumas, surgical exploration seldom necessary
• major
  - laceration that extends into medulla and collecting system, major renal vascular injury, shattered kidney

Etiology
• 80% blunt (MVC, assaults, falls) vs. 20% penetrating (stab wounds and gunshots)

Clinical Features
• mechanism of injury raises suspicion
• can be hemodynamically unstable secondary to renal vascular injury and/or other sustained injuries: ABCs
• upper abdominal tenderness, flank tenderness, flank contusions, lower rib/vertebral transverse process fracture

Investigations
• U/A
  - hematuria: requires workup but degree does not correlate with the severity of injury
• imaging
  - CT (contrast, triphasic) if patient stable: look for renal laceration, extravasation of contrast, retroperitoneal hematoma, and associated intra-abdominal organ injury

Staging (does not necessarily correlate well with clinical status)
• I: contusion/hematoma
• II: <1 cm laceration without urinary extravasation
• III: >1 cm laceration without urinary extravasation
• IV: urinary extravasation
• V: shattered kidney or avulsion of pedicle

Treatment
• microscopic hematuria + isolated well-staged minor injuries → no hospitalization
• gross hematuria + contusion/minor lacerations → hospitalize, bedrest, repeat CT if bleeding persists
• surgical intervention/minimally invasive angiography and embolization
  - absolute indications
    - hemorrhage and hemodynamic instability
relative indications
  • non-viable tissue and major laceration
  • urinary extravasation
  • vascular injury
  • expanding or pulsating peri-renal mass
  • laparotomy for associated injury
• follow-up with U/S or CT before discharge, and at 6 wk

Complications
• HTN in 5% of renal trauma

Bladder Trauma

Classification
• contusions: no urinary extravasation, damage to mucosa or muscularis
• intraperitoneal ruptures: often involve the bladder dome
• extraperitoneal ruptures: involve anterior or lateral bladder wall in full bladder

Etiology
• blunt (MVC, falls, and crush injury) vs. penetrating trauma to lower abdomen, pelvis, or perineum
• blunt trauma is associated with pelvic fracture in 97% of cases

Clinical Features
• abdominal tenderness, distention, peritonitis, and inability to void
• can be hemodynamically unstable secondary to pelvic fracture, other sustained injuries: ABCs
• suprapubic pain

Investigations
• U/A: gross hematuria in 90%
• imaging (including CT cystogram and post-drainage films for extravasation)

Treatment
• penetrating trauma → surgical exploration
• contusion → urethral catheter until hematuria completely resolves
• extraperitoneal bladder perforations → typically non-operative with foley insertion, and follow with cystograms
  ▪ surgery if: infected urine, rectal/vaginal perforation, bony spike into bladder, laparotomy for concurrent injury, bladder neck involvement, persistent urine leak and failed conservative management
• intraperitoneal rupture usually requires surgical repair and suprapubic catheterization

Complications
• complications of bladder injury itself are rare
• mortality is around 20%, and is usually due to associated injuries rather than bladder rupture

Urethral Injuries

Etiology
• posterior urethra
  ▪ common site of injury is junction of membranous and prostatic urethra due to blunt trauma, MVCs, pelvic fracture
  ▪ shearing force on fixed membranous and mobile prostatic urethra
• anterior urethra
  ▪ straddle injury can crush bulbar urethra against pubic rami
• other causes
  ▪ iatrogenic (instrumentation, prosthesis insertion), penile fracture, masturbation with urethral manipulation
• always look for associated bladder rupture

Clinical Features
• blood at urethral meatus
• high-riding prostate on DRE
• swelling and butterfly perineal hematoma
• penile and/or scrotal hematoma
• sensation of voiding without U/O
• distended bladder
Investigations
• must perform RUG or cystoscopy prior to catheterization

Treatment
• simple contusions
  ▫ no treatment
• partial urethral disruption
  ▫ very gentle attempt at catheterization by urologist
  ▫ with no resistance to catheterization → Foley x 2-3 wk
  ▫ with resistance to catheterization → suprapubic cystostomy or urethral catheter alignment in OR
• periodic flow rates/urethrograms to evaluate for stricture formation
• complete disruption
  ▫ immediate repair if patient stable, delayed repair if unstable (suprapubic tube in interim)

Complications
• stricture

Infertility

Definition
• failure to conceive after one year of unprotected, properly timed intercourse
• incidence
  ▫ 15% of all couples
  ▫ ~ 35-40% female, 20% male, 25-30% combined problem

Female Factors
• see Gynecology, GY23

Male Factors

Male Reproduction
• hypothalamic-pituitary-testicular axis (HPTA)
  ▫ pulsatile GnRH from hypothalamus acts on anterior pituitary stimulating release of LH and FSH
  ▫ LH acts on Leydig (interstitial) cells → testosterone synthesis and secretion
  ▫ FSH acts on Sertoli cells → structural and metabolic support to developing spermatogenic cells
  ▫ FSH and testosterone support germ cells (responsible for spermatogenesis)
  ▫ sperm route: epididymis → vas deferens → ejaculatory ducts → prostatic urethra

Etiology
• idiopathic (40-50% infertile males)
• testicular
  ▫ varicocele (35-40% infertile males)
  ▫ tumour
  ▫ congenital (Klinefelter’s triad: small, firm testes, gynecomastia, and azoospermia)
  ▫ post-infectious (epididymo-orchitis, STIs, mumps)
  ▫ uncorrected torsion
  ▫ cryptorchidism (<5% of cases)
• obstructive
  ▫ iatrogenic (surgery; see below)
  ▫ infectious (gonorrhea, chlamydia)
  ▫ trauma
  ▫ congenital (absence of vas deferens, CF)
  ▫ bilateral ejaculatory duct obstruction, epididymal obstructions
  ▫ Kartagener’s syndrome (autosomal recessive disorder causing defect in action of cilia)
• endocrine (see Endocrinology, E48)
  ▫ HPTA (2-3%) e.g. Kallmann’s syndrome (congenital hypothalamic hypogonadism), excess prolactin, excess androgens, excess estrogens
• other
  ▫ retrograde ejaculation secondary to surgery
  ▫ medications
  ▫ drugs: marijuana, cocaine, tobacco, alcohol
  ▫ increased testicular temperature (sauna, hot baths, tight pants or underwear)
  ▫ chronic disease: e.g. liver, renal
  ▫ unexplained infertility
History
- age of both partners
- medical: past illness, DM, trauma, CF, genetic syndromes, STIs, cryptorchidism
- surgical: vasectomy, herniorrhaphy, orchidopexy, prostate surgery
- fertility: pubertal onset, previous pregnancies, duration of infertility, treatments
- sexual: libido, erection/ejaculation, timing, frequency
- family Hx
- medications: cytotoxic agents, GnRH agonists, anabolic steroids, nitrofurantoin, cimetidine, sulfasalazine, spironolactone, α-blockers
- social Hx: alcohol, tobacco, cocaine, marijuana
- occupational exposures: radiation, heavy metals

Physical Exam
- general appearance: sexual development, gynecomastia, obesity
- scrotal exam: size, consistency, and nodularity of testicles; palpation of cord for presence of vas deferens; DRE; Valsalva for varicocele

Investigations
- semen analysis (SA) at least 2 specimens, collected 1-2 weeks apart
  - delivery to lab within 1 hour, 2-7 days of abstinence prior to collection
- hormonal evaluation
  - indicated with abnormal SA (rare to be abnormal with normal SA)
  - testosterone and FSH
  - serum LH and prolactin are measured if testosterone or FSH are abnormal
- genetic evaluation
  - chromosomal studies (Klinefelter’s syndrome – XXY)
  - genetic studies (Y-chromosome microdeletion, CF gene mutation)
- immunologic studies (antisperm antibodies in ejaculate and blood)
- testicular biopsy
- scrotal U/S (varicocele, testicular size)
- vasography (assess patency of vas deferens)

Treatment
- assessment of partner
- lifestyle
  - regular exercise, healthy diet
  - eliminate alcohol, tobacco and illicit drugs
- medical
  - endocrine therapy (see Endocrinology, E49)
  - treat retrograde ejaculation
  - discontinue anti-sympathomimetic agents, may start α-adrenergic stimulation
    (phenylpropanolamine, pseudoephedrine, or ephedrine)
  - treat underlying infections
- surgical
  - varicocelectomy (if indicated)
  - vasovasostomy (vasectomy reversal) or epididymovasostomy
  - transurethral resection of blocked ejaculatory ducts
- assisted reproductive technologies (ART)
  - refer to infertility specialist
  - sperm washing + intrauterine insemination (IUI)
  - in vitro fertilization (IVF)
  - intracytoplasmic sperm injection (ICSI) after CF screening of patient and partner in patients with congenital bilateral absence of vas deferens

Common Terminology on SA
- Teratospermia: Abnormal morphology
- Asthenospermia: Abnormal motility
- Oligospermia: Decreased sperm count
- Azoospermia: Absent sperm in semen
- Mixed types: i.e. oligoasthenospermia

Mutation of cystic fibrosis transmembrane conductance regulator (CFTR) gene is associated with congenital bilateral absence of vas deferens and epididymal cysts, even if patient manifests no symptoms of CF
Pediatric Urology

Congenital Abnormalities

- not uncommon; 1/200 have congenital abnormalities of the GU tract
- six common presentations of congenital urological abnormalities

1. ANTEnatal HYDRONEPHROSIS

Epidemiology
- 1-5% fetal U/S, detectable as early as first trimester
- most common urological consultation in perinatal period and one of most common U/S abnormalities of pregnancy

Differential Diagnosis
- UPJ or UVJ obstruction
- multi-cystic dysplastic kidney
- VUR
- PUVs (only in boys)
- duplication anomalies
- ureteroceles
- ectopic ureter

Treatment
- antenatal in utero intervention rarely indicated unless evidence of PUVs with oligohydramnios

2. POSTERIOR URETHRAL VALVES

Epidemiology
- the most common congenital obstructive urethral lesion in male infants

Pathophysiology
- abnormal mucosal folds at the distal prostatic urethra causing varying degrees of obstruction

Clinical Presentation
- dependent on age
  - antenatal: bilateral hydronephrosis, distended bladder, oligohydramnios
  - neonatal (recognized at birth): palpable abdominal mass (distended bladder, hydronephrosis), ascites (transudation of retroperitoneal urine), respiratory distress (pulmonary hypoplasia from oligohydramnios), weak urinary stream
  - neonatal (not recognized at birth): within weeks present with urosepsis, dehydration, electrolyte abnormalities, failure to thrive

WHO Guidelines

Normal Semen Values
- Volume: 2-5 mL
- Concentration: >15 million sperm/mL
- Morphology: 30% normal forms
- Motility: >40% adequate forward progression
- Liquefaction: complete in 20 min
- pH: 7.2-7.8
- WBC: <10/HPF or <10^6 WBC/mL semen

Majority of antenatal hydronephroses resolve during pregnancy or within the first year of life
- toddlers: UTIs or voiding dysfunction
- school-aged boys: voiding dysfunction → urinary incontinence
- associated findings include renal dysplasia and secondary VUR

**Investigations**
- most commonly recognized on prenatal U/S → bilateral hydronephrosis, thickened bladder, dilated posterior urethra ("keyhole sign"), oligohydramnios in a male fetus
- VCUG → dilated and elongated posterior urethra, trabeculated bladder, VUR

**Treatment**
- immediate catheterization to relieve obstruction, followed by cystoscopic resection of PUV when baby is stable
- if resection of PUV is not possible, vesicostomy is indicated

### 3. URETEROPELVIC JUNCTION OBSTRUCTION

**Etiology**
- unclear: adynamic ureteral segment, stenosis, strictures, extrinsic compression, stenosis, strictures, aberrant blood vessels
- can rarely be secondary to tumour, stone, etc, in children

**Epidemiology**
- the most common congenital defect of the ureter
- M:F = 2:1
- up to 40% bilateral, which may be associated with worse prognosis

**Clinical Presentation**
- symptoms depend on severity and age at diagnosis (mostly asymptomatic finding on antenatal U/S)
  - infants: abdominal mass, urinary infection
  - children: pain, vomiting, failure to thrive
- some cases are diagnosed after puberty and into adulthood
  - in adolescents and adults, the symptoms may be triggered by episodes of increased diuresis, such as following alcohol ingestion (Dietl's crisis)

**Investigations**
- antenatal U/S most common, Doppler U/S (rare), IVP (rare), and renal scan ± furosemide

**Treatment**
- surgical correction (pyeloplasty), consider nephrectomy if <15% differential renal function

### 4. VESICOURETERAL REFLUX

**Definition**
- retrograde passage of urine from the bladder, through the UVJ, into the ureter

**Classification**
- primary reflux: incompetent or inadequate closure of UVJ
  - lateral ureteral insertion, short submucosal segment
- secondary reflux: abnormally high intravesical pressure resulting in failure of UVJ closure
  - often associated with anatomic (PUV) or functional (neuropathic) bladder obstruction

**Epidemiology**
- estimated ~1% of newborns, but not well known
- incidence and clinical relevance higher in children with febrile UTIs and prenatal hydronephrosis
- risk factors: race (white > black), female gender, age (<2 yr), genetic predisposition

**Investigations**
- focused Hx, particularly of voiding dysfunction (frequency, urgency, diurnal enuresis, constipation, encopresis)
  - also screen for signs of infection (UTI, pyelonephritis, urosepsis) and renal failure (uremia, HTN)
- initial evaluation of renal status, growth parameters, and blood pressure is warranted in any child with VUR due to high incidence of renal scarring
  - height, weight, blood pressure
  - Cr
  - U/A, C&S
  - renal U/S
- DMSA renal scan if at high risk (greater sensitivity in detecting structural defects associated with dysplasia, renal scarring or pyelonephritis; entails radiation exposure)
- family screening is controversial
Treatment
• spontaneous resolution in 60% of primary reflux
  ▪ in lower grades (I-III), goal is to prevent infection or renal damage via medical treatment
  and monitoring
• medical treatment: daily ABx prophylaxis at half the treatment dose for acute infection (see Table 9 - TMP/SMX, trimethoprim, amoxicillin, or nitrofurantoin)
• surgical treatment: ureteral reimplantation ± ureteroplasty, or subureteral injection with bulking agents (DeFlux® or Macroplastique®)
  ▪ indications include failure of medical management, renal scarring (e.g. renal insufficiency, HTN), breakthrough UTIs, persistent high grade (IV or V) reflux

5. HYPOSPADIAS
Definition
• a condition in which the urethral meatus opens on the ventral side of the penis, proximal to the normal location in the glans penis
• depending on severity, may result in difficulty directing urinary stream, having intercourse or depositing sperm in vagina

Epidemiology
• very common; 1/300 live male births
• distal hypospadias more common than proximal
• white >> black
• may be associated with ventral penile curvature, disorders of sexual differentiation, undescended testicles or inguinal hernia

Treatment
• early surgical correction; optimal repair before 2 yr
• neonatal circumcision should be deferred because the foreskin may be utilized in the correction

6. EPISPADIAS-EXSTROPHY COMPLEX
Definition
• a spectrum of defects depending on the timing of the rupture of the cloacal membrane
  ▪ bladder extrophy: congenital absence of a portion of lower abdominal and anterior bladder wall, with exposure of the bladder lumen
  ▪ cloacal extrophy
    • exposed bladder and bowel with imperforate anus
    • associated with spina bifida in >50%
  ▪ epispadias (least severe)
    • urethra opens on dorsal aspect of the penis, often associated with penile curvature

Etiology
• represents failure of closure of the cloacal membrane, resulting in the bladder and urethra opening directly through the abdominal wall

Epidemiology
• rare: incidence 1/30,000, M:F = 3:1 predominance
• high morbidity → multiple reconstructive surgeries, incontinence, infertility, reflux

Treatment
• surgical correction at birth
• later corrections for incontinence, VUR, and low bladder capacity may be needed

Nephroblastoma (Wilms’ Tumour)
Etiology
• arises from abnormal proliferation of metanephric blastema

Epidemiology
• 5% of all childhood cancers, 5% bilateral
• most common primary malignant renal tumour of childhood
• average age of incidence is 3 yr
Clinical Features
- abdominal mass: large, firm, unilateral (80%)
- HTN (25%)
- flank tenderness
- microscopic hematuria
- nausea/vomiting

Treatment
- always investigate contralateral kidney and renal vein (for tumour thrombus)
- unilateral disease: radical nephrectomy ± radiation ± chemotherapy
- bilateral disease: nephron-sparing surgery following neoadjuvant chemotherapy

Prognosis
- 5 yr survival 80%

Cryptorchidism/Ectopic Testes

Definition
- abnormal location of testes somewhere along the normal path of descent (external inguinal ring > inguinal canal > abdominal)
- ectopic testis (testis found outside its normal path of descent) is most commonly located within a superficial pouch between the external oblique fascia and Scarpa’s fascia (Denis Browne pouch)
- differential diagnosis:
  - retractile testes
  - atrophic testes
  - disorders of sexual differentiation (bilateral impalpable gonads)

Epidemiology
- 2.7% of full term newborns
- 0.7-0.8% at 1 yr

Treatment
- orchiopexy
- hormonal therapy not proven to be of benefit over standard surgical treatment

Prognosis
- reduction in fertility
  - untreated bilateral cryptorchidism: ~100% infertility
  - paternity rates: 53%, 90%, and 93% in formerly bilateral cryptorchid, formerly unilateral cryptorchid, and normal men, respectively
- increased malignancy risk
  - intraabdominal > inguinal
  - surgical correction facilitates testicular monitoring and may reduce malignancy risk
- increased risk of testicular torsion (reduced by surgical correction)

Disorders of Sexual Differentiation

Definition
- formerly known as intersex disorders
- abnormal genitalia for chromosomal sex due to the undermasculinization of males or the virilization of females
- considered a social emergency

Classification
1. 46 XY DSD
   - defect in testicular synthesis of androgens
   - androgen resistance in target tissues
   - palpable gonad
2. 46 XX DSD
   - most due to CAH (21-hydroxylase deficiency most common enzymatic defect) → shunt in steroid biosynthetic pathway leading to excess androgens
   - undiagnosed and untreated CAH can be associated with life-threatening electrolyte abnormalities in the newborn (salt-wasting CAH)
3. ovotesticular DSD
4. mixed gonadal dysgenesis (46 XY/45 XO most common karyotype)
   - presence of Y chromosome → partial testis determination to varying degrees
Diagnosis
• thorough family Hx noting any consanguinity
• maternal Hx, especially medication/drug use during pregnancy (maternal hyperandrogenemia)
• P/E: palpable gonad (= chromosomal male), hyperpigmentation, evidence of dehydration, HTN, stretched phallus length, position of urethral meatus
• laboratory tests
  ▪ plasma 17-OH-progesterone (after 36 h of life) → increased in 21-hydroxylase deficiency (CAH)
  ▪ plasma 11-deoxycortisol → increased in 11-β-hydroxylase deficiency
  ▪ basal adrenal steroid levels
  ▪ serum testosterone and DHT pre- and post-hCG stimulation (2,000 IU/d for 4 d)
  ▪ serum electrolytes
  ▪ chromosomal evaluation including sex karyotype
• U/S of adrenals, gonads, uterus, and fallopian tubes
• endoscopy and genitography of urogenital sinus

Treatment
• steroid supplementation as indicated (e.g. CAH)
• sex assignment after extensive family consultation
  ▪ must consider capacity for sexually functioning genitalia in adulthood, fertility potential, and psychological impact
• reconstruction of external genitalia between 6 and 12 mo
• long-term psychological guidance and support for both patient and family

Enuresis
• see Pediatrics, P9

Selected Urological Procedures

Bladder Catheterization
• catheter size measured by the French (Fr) scale – circumference in mm
• each 1 mm increase in diameter = approximately 3 Fr increase (standard size 16-18 Fr)
• should be removed as soon as possible to reduce the risk of UTI

Continuous Catheterization
• indications
  ▪ accurate monitoring of U/O
  ▪ relief of urinary retention due to medication, neurogenic bladder, or intravesical obstruction
  ▪ temporary therapy for urinary incontinence
  ▪ perineal wounds
  ▪ clot prevention (24-28 Fr) for CBI
  ▪ post-operative

Alternatives to Continuous Catheterization
• intermittent catheterization
  ▪ PVR measurement
  ▪ to obtain sterile diagnostic specimens for U/A, urine C&S
  ▪ management of neurogenic bladder or chronic urinary retention
• condom catheter
• suprapubic catheter

Causes of Difficult Catheterizations and Treatment
• patient discomfort → use sufficient lubrication (± xylocaine)
• collapsing catheter → lubrication as above ± firmer or larger catheter (silastic catheter)
• meatal/urethral stricture → dilate with progressively larger catheters/balloon catheter
• BPH → use coudé catheter as angled tip can help navigate around enlarged prostate
• urethral disruption/obstruction → filiform and followers or suprapubic catheterization
• anxious patient → anxiolytic medication

Complications of Catheterization
• infection: UTI
• meatal/urethral trauma
Circumcision

Definition
• removal of some or all of the foreskin from the penis

Epidemiology
• 30% worldwide
• frequency varies depending on geographic location, religious affiliation, socioeconomic classification

Medical Indications
• phimosis and recurrent paraphimosis
• recurrent UTIs (particularly in infants and in association with other urinary abnormalities)
• balanitis xerotica obliterans or other chronic inflammatory conditions

Contraindications
• unstable or sick infant
• congenital genital abnormalities (hypospadias)
• family Hx of bleeding disorders warrants laboratory investigation prior to circumcision

Complications
• bleeding
• infection
• penile entrapment, skin bridges
• fistula
• glans injury
• penile sensation deficits

Cystoscopy

Objective
• endoscopic inspection of the lower urinary tract (urethra, prostate, bladder, and ureteral orifices), samples for cytology
• scopes can be flexible or rigid

Indications
• gross hematuria
• LUTS (storage or voiding)
• urethral and bladder neck strictures
• bladder stones
• bladder tumour surveillance
• evaluation of upper tracts with retrograde pyelography (ureteric stents, catheters)

Complications
• during procedure
  ▪ bleeding
  ▪ anesthetic-related
  ▪ perforation (rare)
• post-procedure (short-term)
  ▪ infections, e.g. epididymo-orchitis (rare)
  ▪ urinary retention
• post-procedure (long-term)
  ▪ stricture

Circumcision Status and Risk of HIV and Sexually Transmitted Infections among Men who have Sex with Men: A Meta-Analysis

Purpose: To describe the association between male circumcision and HIV infection and other sexually transmitted infections (STIs) among men who have sex with men (MSM).

Methods: Meta-analysis of 15 studies (n=53,567)

Results: The associations between circumcision and HIV-positive and STIs were not statistically significant. Male circumcision had a protective association with HIV in studies of MSM conducted before the introduction of highly active anti-retroviral therapy.

Conclusions: There is insufficient evidence to support that male circumcision protects against HIV infection or other STIs.

Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men
Cochrane DB Syst Rev 2009;2:CD003362

Purpose: To evaluate the effectiveness and safety of male circumcision for preventing acquisition of HIV in heterosexual men.

Methods: The analyzed data is from three randomized controlled trials to assess the efficacy of male circumcision for preventing HIV acquisition in men in Africa.

Results: Medical male circumcision reduces the acquisition of HIV by heterosexual men (30%-66% over 24 mo).

Male Circumcision for Prevention of Heterosexual Acquisition of HIV in Men

Study: Guidelines by the American Academy of Pediatrics (AAP).

Recommendations: The American Academy of Pediatrics radically changed their position on male circumcision in 2012. The report from the AAP now states that the preventative health benefits outweigh the risks of the procedure and that the procedure is well-tolerated with adequate pain management and sterility. Stated benefits include the prevention of urinary tract infection, penile cancer, transmission of some sexually transmitted infections, including HIV. There is believed to be no effect on penile sexual function, sensitivity or sexual satisfaction. Acute complications are rare and more common if the procedure is done by an untrained provider.

Note: The Canadian Pediatric Society (CPS) has not yet updated their position on male circumcision since 1996, which stated that the CPS is opposed to routine circumcision. A new statement is expected soon.
Radical Prostatectomy

**Objective**
- the removal of the entire prostate and prostatic capsule via a lower midline abdominal incision, laparoscopically or robotically
  - internal iliac and obturator vessel lymph nodes may also be dissected and sent for pathology (dependent on risk: clinical stage, grade, PSA)
  - seminal vesicle vessels are also partially or completely removed

**Indications**
- treatment for localized prostate cancer

**Complications**
- immediate (intraoperative)
  - blood loss
  - rectal injury (extremely rare)
  - ureteral injury (extremely rare)
- perioperative
  - lymphocele formation
- late
  - moderate to severe urinary incontinence (3-10%)
  - mild urinary incontinence (20%)
  - ED (~50%, depending on whether one, both, or neither of the neurovascular bundles are involved in extracapsular extension of tumour)

Transurethral Resection of the Prostate

**Objective**
- to partially resect the periurethral portion of the prostate (transition zone) to decrease symptoms of urinary tract obstruction
- accomplished via a transurethral (cystoscopic) approach using an electrocautery loop, irrigation (glycine), and illumination

**Indications**
- obstructive uropathy (large bladder diverticula, renal insufficiency)
- refractory urinary retention
- recurrent UTIs
- recurrent gross hematuria
- bladder stones
- intolerance/failure of medical therapy

**Complications**
- acute
  - intra- or extraperitoneal rupture of the bladder
  - rectal perforation
  - incontinence
  - incision of the ureteral orifice (with subsequent reflux or ureteral stricture)
  - hemorrhage
  - epididymitis
  - sepsis
  - transurethral resection syndrome (also called “post-TURP syndrome”)
    - caused by absorption of a large volume of the hypotonic irrigation solution used, usually through perforated venous sinusoids, leading to a hypervolemic hyponatremic state
    - characterized by dilutional hyponatremia, confusion, nausea, vomiting, HTN, bradycardia, visual disturbances, CHF, and pulmonary edema
    - treat with diuresis and (if severe) hypertonic saline administration
- chronic
  - retrograde ejaculation (>75%)
  - ED (5-10% risk increases with increasing use of cautery)
  - incontinence (<1%)
  - urethral stricture
  - bladder neck contracture


**Study**: A systematic review to compare perioperative outcomes, positive surgical margin (PSM) rates, and functional outcomes in retropubic radical prostatectomy (RRP) laparoscopic RP (LRP) and robot-assisted radical prostatectomy (RARP).

**Methods**: Medline database was searched. Weighted means (based on number of participants in each study) were calculated for all outcomes.

**Results**: 58 articles were reviewed. LRP and RARP were associated with better perioperative outcomes compared to RRP. LRP and RARP had similar post-operative complication rates ranging from 10.3-10.98%. RARP had a lower overall PSM rate than LRP, and RRP. RARP had the highest continence rate and mean potency rates.

**Conclusion**: In high-volume centers, RRP, LRP and RARP are safe options for treating patients with localized prostate cancer. LRP and RARP are associated with better perioperative outcomes and RARP showed lower PSM rates, higher potency and continence compared to RRP and LRP.
Extracorporeal Shock Wave Lithotripsy

Objective
- to treat renal and ureteral calculi (proximal, middle or distal) which cannot pass through the urinary tract naturally
- shockwaves are generated and focused onto stone → fragmentation, allowing stone fragments to pass spontaneously and less painfully

Indications
- potential first-line therapy for renal and ureteral calculi <2.5 cm
- individuals with calculi in solitary kidney
- individuals with HTN, DM or renal insufficiency
*patient preference and wait-times play a large role in stone management

Contraindications
- acute UTI or urosepsis
- bleeding disorder or coagulopathy
- pregnancy
- obstruction distal to stone

Complications
- bacteriuria
- bacteremia
- post-procedure hematuria
- ureteric obstruction (by stone fragments)
- peri-nephric hematoma

Common Medications

Table 27. Erectile Dysfunction Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>sildenafil</td>
<td>Phosphodiesterase 5 inhibitor</td>
<td>Severe hypotension (very rare)</td>
</tr>
<tr>
<td>tadalafil</td>
<td>Selective inhibition of PDE5 (enzyme which degrades cGMP)</td>
<td>Contraindicated if Hx of priapism, or in conditions predisposing to priapism (leukemia, myelofibrosis, polycythemia, sickle cell disease)</td>
</tr>
<tr>
<td>vardenafil</td>
<td>Leads to sinusoidal smooth muscle relaxation and erection</td>
<td>Contraindicated with nitrates</td>
</tr>
<tr>
<td>(PDE5is for use when some erection present)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>alprostadil (MUSE®), PGE1 + phentolamine + papaverine mixture</td>
<td>Prostaglandin E1 activation of cAMP, relaxing sinusoidal smooth muscle Local release (capsule inserted into urethra)</td>
<td>Penile pain Presyncope</td>
<td></td>
</tr>
<tr>
<td>triple therapy also used: papaverine, phentolamine, PGE1</td>
<td>See above</td>
<td>See above</td>
<td>Thinning of tunica albuginea at site of repeated injections (Peyronie’s plaque) Painful erection Hematoma Contraindicated if Hx of priapism, or in conditions predisposing to priapism</td>
</tr>
</tbody>
</table>

Table 28. Benign Prostatic Hyperplasia Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>terazosin</td>
<td>a1 blockers</td>
<td>α1-adrenergic antagonists reduce stromal smooth muscle tone</td>
<td>Presyncope Leg edema</td>
</tr>
<tr>
<td>doxazosin</td>
<td></td>
<td>Reduce dynamic component of bladder outlet obstruction</td>
<td>Retrograde ejaculation Headache Asthenia Nasal congestion</td>
</tr>
<tr>
<td>tamsulosin</td>
<td>α1A selective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alfuzosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>silodosin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>finasteride</td>
<td>5α-reductase inhibitor</td>
<td></td>
<td>Sexual dysfunction PSA decreases</td>
</tr>
<tr>
<td>dutasteride</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Table 29. Prostatic Carcinoma Medications (N>0, M>0)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>leuprolide, goserelin</td>
<td>GnRH agonist</td>
<td>Initially stimulates LH, increasing testosterone and causing “flare” (initially increases bone pain) Later causes low testosterone</td>
<td>Hot flashes Headache Decreased libido</td>
</tr>
<tr>
<td>*diethylstilbestrol (DES)</td>
<td>Estrogens</td>
<td>Inhibit LH and cytotoxic effect on tumour cells</td>
<td>Increased risk of cardiovascular events (no longer available commercially in North America)</td>
</tr>
<tr>
<td>*cyproterone acetate</td>
<td>Steroidal antiandrogen</td>
<td>Competes with DHT for intracellular receptors: 1. Prevent flare produced by GnRH agonist 2. Use for complete androgen blockade 3. May preserve potency</td>
<td></td>
</tr>
<tr>
<td>flutamide, bicalutamide</td>
<td>Non-steroidal antiandrogen</td>
<td>As above</td>
<td>Hepatotoxic: AST/ALT monitoring</td>
</tr>
<tr>
<td>*ketoconazole, spironolactone</td>
<td>Steroidogenesis inhibitors</td>
<td>Blocks multiple enzymes in steroid pathway, including adrenal androgens</td>
<td>GI symptoms Hyperkalemia Gynecomastia</td>
</tr>
</tbody>
</table>

*Very rarely used

## Table 30. Continence Agents and Overactive Bladder Medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Mechanism</th>
<th>Indication</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>oxybutynin</td>
<td>Antispasmodic</td>
<td>Inhibits action of ACh on smooth muscle Decreases frequency of uninhibited detrusor contraction Diminishes initial urge to void</td>
<td>Overactive bladder Urge incontinence + urgency + frequency</td>
<td>Dry mouth Blurred vision Constipation Supraventricular tachycardia</td>
</tr>
<tr>
<td>oxybutynin, tolterodine, trospium, solifenacin, darifenacin fesoterodine</td>
<td>Anticholinergic</td>
<td>Muscarinic receptor antagonist Selective for bladder Increases bladder volume Decreases detrusor pressure</td>
<td>Overactive bladder Urge incontinence + urgency + frequency</td>
<td>As above</td>
</tr>
<tr>
<td>mirabegron</td>
<td>ß3 agonist</td>
<td>Beta sympathetic receptor blocker in the bladder; relaxes bladder during storage phase</td>
<td>Overactive bladder Urge incontinence + urgency + frequency</td>
<td>Blood pressure should be monitored</td>
</tr>
<tr>
<td>imipramine</td>
<td>Tricyclic antidepressant</td>
<td>Sympathomimetic effects: urinary sphincter contraction Anticholinergic effects: detrusor relaxation</td>
<td>Stress and urge incontinence</td>
<td>As above Weight gain Orthostatic hypotension Prolonged PR interval</td>
</tr>
</tbody>
</table>

Note: All anti-cholinergics are equally effective and long-acting formulations are better tolerated. Newer muscarinic M3 receptor specific agents (solifenacin, darifenacin) are equally efficacious as older drugs, however, RCTs based on head-to-head comparison to long acting formulations are lacking.
References

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Overactive Bladder


Benign Renal Neoplasm


Urological Emergencies


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EBM


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Acronyms

AAA  abdominal aortic aneurysm
ABI  ankle-brachial index
ACEI  angiotensin converting enzyme inhibitor
AFib atrial fibrillation
AKA above-knee amputation
AKI  acute kidney injury
daPTT activated partial thromboplastin time (i.e. PTT)
ASA acetylsalicylic acid (Aspirin®)
AT anterior tibial artery
BKA below-knee amputation
BP blood pressure
CABG coronary artery bypass graft
CAD coronary artery disease
CBC complete blood count
CCB calcium channel blocker
CLI critical limb ischemia
CTA computed tomography angiography
CVD cerebrovascular disease
CVI chronic venous insufficiency
CXR chest x-ray
disseminated intravascular coagulation
diabetes mellitus
deep vein thrombosis
displaced coated ASA
electrocardiogram
cholesterol
essential thrombocythemia
endovascular aortic aneurysm repair
endovenous laser therapy
greater saphenous vein
hepatic-induced thrombocytopenia with thrombosis
hypertension
inflammatory bowel disease
international normalized ratio
low molecular weight heparin
lesser saphenous vein
MCA middle cerebral artery
MRA magnetic resonance angiography
MSK musculoskeletal
OCP oral contraceptive pill
PE pulmonary embolism
PTT partial thromboplastin time (i.e. aPTT)
PVD peripheral vascular disease
RIND reversible ischemic neurologic deficit
SFA superficial femoral artery
SVA superficial venous thrombosis
TAA thoracic aortic aneurysm
TEE transesophageal echocardiography
TIA transient ischemic attack
TIA thoracic endovascular aortic aneurysm repair
TTE thoracic echocardiography

Vascular Surgery

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Peripheral Arterial Disease

Chronic Arterial Occlusion/Insufficiency

Definition
- chronic ischemia due to inability of the arterial supply to meet cellular metabolic demands

Etiology
- predominantly due to atherosclerosis (for pathogenesis, see Cardiology, C26); primarily occurs in the lower extremities

Risk Factors
- major: smoking, DM
- minor: HTN, hyperlipidemia, obesity, sedentary lifestyle, PMHx or FMHx CAD/CVD

Clinical Features
- claudication - must differentiate vascular from neurogenic claudication (see Table 1)
  1. pain with exertion: usually in calves or any exercising muscle group
  2. relieved by short rest: 2-5 min, and no postural changes necessary
  3. reproducible: same distance to elicit pain, same location of pain, same amount of rest to relieve pain
- critical limb ischemia (CLI)
  1. includes rest pain, night pain, tissue loss (ulceration or gangrene)
  2. pain most commonly over the forefoot, waking person from sleep, and often relieved by hanging foot off bed
  3. ankle pressure <40 mmHg, toe pressure <30 mmHg, ABI <0.40
- pulses may be absent at some locations, bruits may be present
- signs of poor perfusion: hair loss, hypertrophic nails, atrophic muscle, skin ulcerations and infections, slow capillary refill, prolonged pallor with elevation and rubor on dependency, venous troughing (collapse of superficial veins of foot)
- other manifestations of atherosclerosis: CVD, CAD, impotence, splanchnic ischemia

Differential Diagnosis of Claudication

Vascular
- Atherosclerotic disease
- Vasculitis (e.g. Buerger’s disease, Takayasu’s arteritis)
- Diabetic neuropathy
- Venous disease (e.g. DVT, varicose veins)
- Popliteal entrapment syndrome (e.g. Baker’s cyst, tumour)

Neurogenic
- Neurospinal disease (e.g. spinal stenosis)
- Reflex sympathetic dystrophy

MSK
- OA
- Rheumatoid arthritis/connective tissue disease
- Remote trauma
Table 1. Clinical Categories of Acute Limb Ischemia

<table>
<thead>
<tr>
<th>Pulsiating Factors</th>
<th>Vascular Claudication</th>
<th>Neurogenic Claudication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provoking Factors</td>
<td>Walking uphill</td>
<td>Walking downhill</td>
</tr>
<tr>
<td>Puls/Bis</td>
<td>Reduced</td>
<td>Normal</td>
</tr>
<tr>
<td>Pain on Bicycling</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Motor Weakness</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Skin Changes</td>
<td>Present</td>
<td>Absent</td>
</tr>
</tbody>
</table>

Investigations
- non-invasive
- routine blood work, fasting metabolic profile
- ABI: take highest brachial and highest ankle (dorsalis pedis artery or posterior tibial artery) pressures for each side generally
  - ABI <0.90 abnormal, rest pain appears at <0.30 (see Table 3)
- CTA and MRA
  - excellent for large arteries (aorta, iliac, femoral, popliteal) may have difficulty with tibial arteries (especially in the presence of disease)
  - require IV injection of nephrotoxic contrast (iodinated contrast for CT, gadolinium for MR)
  - used primarily for planning interventions
- invasive arteriography: superior resolution to CTA/MRA, better for tibial arteries, can be done intraoperatively

Table 2. Ankle-Brachial Indices

<table>
<thead>
<tr>
<th>ABI Recording</th>
<th>Degree of Ischemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;1.20</td>
<td>Suspect wall calcification (most common in diabetics)</td>
</tr>
<tr>
<td>&gt;0.95</td>
<td>Normal/no ischemia</td>
</tr>
<tr>
<td>0.50-0.80</td>
<td>Claudication range</td>
</tr>
<tr>
<td>&lt;0.40</td>
<td>Possible critical ischemia</td>
</tr>
</tbody>
</table>

Treatment
- conservative
  - risk factor modification (smoking cessation, HbA1c control, treatment of HTN, hyperlipidemia (statin), antiplatelet therapy [ECASA])
  - exercise program (30 min 3x/wk): improves collateral circulation, oxygen extraction at the muscle level
  - foot care (especially in DM): keep wounds clean/dry, avoid trauma and pressure on wounds
- pharmacotherapy
  - antiplatelet agents (e.g. ECASA, clopidogrel)
  - cilostazol (cAMP-phosphodiesterase inhibitor with antiplatelet and vasodilatory effects): improves walking distance for some patients with claudication (not available in Canada)
- surgical/endovascular
  - indications: severe lifestyle impairment, vocational impairment, critical ischemia
  - surgical options
    - endovascular (stenting/angioplasty)
    - endarterectomy: removal of plaque and repair with patch (usually distal aorta or common/profunda femoral)
    - bypass graft sites: aortofemoral, axillofemoral, femoropopliteal, distal arterial – graft choices: vein graft (reversed or in situ), synthetic (polytetrafluoroethylene graft (e.g. Gore-Tex®) or Dacron®)
    - amputation: if not suitable for revascularization, persistent serious infections/gangrene

Prognosis
- claudication: conservative therapy: 60-80% improve, 20-30% stay the same, 5-10% deteriorate, 5% will require intervention within 5 yr, <4% will require amputation
- for patients with CLI (rest pain, night pain, ulceration or gangrene): high risk of limb loss (which carries 25% risk of death at 1 yr)

Acute Arterial Occlusion/Insufficiency

Definition
- acute occlusion/rupture of a peripheral artery, usually without a history of claudication
- urgent management required
  - skeletal muscle can tolerate 6 h of ischemia before or irreversible damage and myonecrosis result, exception is in acute-on-chronic occlusion, because the build up of collaterals allows time to investigate
  - tends to be lower extremity > upper extremity; femoropopliteal > aortoiliac
Etiology and Risk Factors

- embolism (examples of pro-embolic conditions are cardiac arrhythmias, endocarditis, and arterial aneurysms)
- existing atherosclerotic plaques (ie chronic PAD) can rupture causing occlusion
- hypercoagulable states can contribute to arterial thrombosis

Clinical Features

Table 3. Arterial Embolism vs. Thrombosis

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Embolus</th>
<th>Thrombus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>Acute</td>
<td>Progressive, acute-on-chronic</td>
</tr>
<tr>
<td>Loss of Function/Sensation</td>
<td>Prominent</td>
<td>Less profound (due to underlying collaterals)</td>
</tr>
<tr>
<td>Hx of Claudication</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Atrophic Changes</td>
<td>No</td>
<td>Maybe</td>
</tr>
<tr>
<td>Contralateral Limb Pulses</td>
<td>Classically normal</td>
<td>Decreased or absent</td>
</tr>
</tbody>
</table>

Investigations

- history and physical exam are essential: depending on degree of ischemia one may have to forego investigations and go straight to the operating room
- ABI: extension of physical exam, easily performed at bedside
- ECG, troponin: rule out recent MI or arrhythmia
- CBC: rule out leukocytosis, thrombocytosis or recent drop in platelets in patients receiving heparin
- PT/INR: patient anticoagulated/sub-therapeutic INR
- Echo: identify wall motion abnormalities, intracardiac thrombus, valvular disease, aortic dissection (Type A)
- CT angiogram: underlying atherosclerosis, aneurysm, aortic dissection
- conventional catheter based angiography: can be obtained in OR; prelude to thrombolytics

Table 4. Clinical Categories of Acute Limb Ischemia

<table>
<thead>
<tr>
<th>Grade</th>
<th>Category</th>
<th>Sensory Loss</th>
<th>Motor Deficit</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Viable</td>
<td>None</td>
<td>None</td>
<td>No immediate threat</td>
</tr>
<tr>
<td>IIA</td>
<td>Marginally threatened</td>
<td>None or minimal (toes)</td>
<td>None</td>
<td>Salvageable if promptly treated</td>
</tr>
<tr>
<td>IIB</td>
<td>Immediately threatened</td>
<td>More than toes</td>
<td>Mild/moderate</td>
<td>Salvageable if promptly revascularized</td>
</tr>
<tr>
<td>III</td>
<td>Irreversible</td>
<td>Profound, anesthetic</td>
<td>Profound, paralysis (rigor)</td>
<td>Major tissue loss Amputation Permanent nerve damage inevitable</td>
</tr>
</tbody>
</table>

Treatment

- immediate heparinization with 5000 IU bolus and continuous infusion to maintain PTT >60 s
- if impaired neurovascular status: emergent revascularization
- if intact neurovascular status: time for work up (including angiogram)
- definitive treatment
  - embolus: embolectomy
  - thrombus: thrombectomy ± bypass graft ± endovascular therapy
  - irreversible ischemia (complete loss of power or sensation, absent venous and arterial dopplers, rigor): primary amputation
- identify and treat underlying cause
- continue heparin post-operatively, start warfarin post-operative day 1 x 3 mo depending on underlying etiology

Complications

- compartment syndrome with prolonged ischemia; requires 4-compartment (anterior/lateral/superficial and deep posterior) fasciotomy
- risk of arrhythmia and death with reperfusion injury
- renal failure and multi-organ failure due to toxic metabolites from ischemic muscle

Prognosis

- 12-15% mortality rate
- 5-40% morbidity rate (amputation)
Aortic Disease

Aortic Dissection

Definition
- tear in aortic intima allowing blood to dissect into the media
- Stanford classification: Type A (involve the ascending aorta) vs. Type B (do not)
- DeBakey Classification
  - Type I: involves the ascending aorta, aortic arch, and descending aorta
  - Type II: confined to the ascending aorta
  - Type III: confined to the descending aorta distal to the left subclavian artery
- acute <2 wk (initial mortality 1% per hour for Type A dissections)
- chronic >2 wk (mortality levels up to 75-80%)

Etiology
- most common: HTN → degenerative/cystic changes → damage to aortic media
- other: connective tissue disease (e.g. Marfan’s, Ehlers-Danlos), cystic medial necrosis, atherosclerosis, congenital conditions (e.g. coarctation of aorta, bicuspid aortic valves, patent ductus arteriosus), infection (e.g. syphilis), trauma, arteritis (e.g. Takayasu’s)

Epidemiology
- incidence of 5.2 in 1,000,000
- M:F = 3:2:1
- small increased incidence in African-Canadians (related to higher incidence of HTN)
- lowest incidence in Asians
- peak incidence 50-65 yr old; 20-40 yr old with connective tissue diseases

Clinical Features
- sudden onset tearing chest pain that radiates to back with:
  - HTN (75-85% of patients)
  - asymmetric BPs and pulses between arms (>30 mmHg difference indicates poor prognosis)
  - ischemic syndromes due to occlusion of aortic branches: coronary (MI), carotid (ischemic stroke, Horner’s syndrome), splanchic (mesenteric ischemia), renal (AKI), peripheral (ischemic leg), intercostal vessels (spinal cord ischemia)
  - “unseating” of aortic valve cusps (new diastolic murmur in 20-30%) in Type A dissection
  - rupture into pleura (dyspnea, hemothorax) or peritoneum (hypotension, shock) or pericardium (cardiac tamponade)
  - syncope

Investigations
- CXR
  - pleural cap (pleural effusion in lung apices)
  - widened mediastinum
  - left pleural effusion with extravasation of blood
- TEE: can visualize aortic valve and thoracic aorta but not abdominal aorta
- ECG: LVH ± ischemic changes, pericarditis, heart block
- CTA (gold standard), aortography, MRA: 100% sensitive and specific
- blood work: lactate (elevated in ischemic gut, shock), amylase (rule out pancreatitis), troponin (rule out MI)

Treatment
- pharmacologic
  - β-blocker to lower BP and decrease cardiac contractility
  - use nondihydropyridine CCB if there is a clear contraindication to β-blockers
  - target sBP of 110 mmHg and HR <60 bpm
  - ACEI and/or other vasodilators if insufficient BP or HR control
- surgical
  - urgent surgical consult if thoracic aortic dissection diagnosed or highly suspected
  - Type A to cardiac surgery, Type B to vascular surgery
  - resection of segment with intimal tear
  - reconstitution of flow through true lumen
  - replacement of the affected aorta with prosthetic graft
  - correction of any predisposing factors
  - post-operative complications: renal failure, intestinal ischemia, stroke, paraplegia, persistent leg ischemia, death
  - 2/3 of patients die of operative or post-operative complications

Figure 3. Aortic anatomy
**Aortic Aneurysm**

**Definition of Aneurysm**
- localized dilatation of an artery having a diameter at least 1.5x that of the expected normal diameter
  - true aneurysm: involving all vessel wall layers (intima, media, adventitia)
  - false aneurysm (also known as pseudo-aneurysm): disruption of the aortic wall or the anastomotic site between vessel and graft with containment of blood by a fibrous capsule made of surrounding tissue
- aneurysms can rupture, thrombose, embolize, erode, and fistulate

**Classification**
- thoracic aortic aneurysm (TAA): ascending, transverse arch, descending
- thoracoabdominal
- abdominal aortic aneurysm (AAA): 90-98% are infrarenal
  - suprarenal: involves one or more visceral arteries, but does not involve the chest
  - pararenal: renal arteries arise from aneurysmal aorta, but the SMA origin is not aneurysmal
  - juxtarenal: the renal arteries originate from normal aorta, but are immediately adjacent to aneurysmal aorta (there is no nonaneurysmal aorta distal to the origin of the renal arteries)
- infrarenal: The aneurysm originates distal to the renal arteries (there is nonaneurysmal aorta distal to the origins of the renal arteries)

**Etiology**
- degenerative (atherosclerotic)
- traumatic
- mycotic (*Salmonella, Staphylococcus*, usually suprarenal aneurysms)
- connective tissue disorder (Marfan syndrome, Ehlers-Danlos syndrome)
- vasculitis
- infectious (syphilis, fungal)
- ascending thoracic aneurysms are associated with bicuspid aortic valve
- risk factors: smoking, HTN, age >70, family history

**Epidemiology**
- incidence 4.7 to 31.9 per 100,000 for AAA and 5.9 per 100,000 for TAA
- high risk groups
  - ≥65 yr
  - M:F = 3.8:1
  - PVD, CAD, CVD
  - family history of AAA

**Figure 4. Classification of aortic dissection** (black arrow indicates where the dissection begins)

- **DeBakey:**
  - Type I: 50%
  - Type II: 35%
- **Stanford:**
  - Type A
  - Type B

**ACC/AHA 2005 Guidelines** define an AAA when the minimum AP diameter of abdominal aorta ≥3.0 cm

**Figure 5. Classification of aneurysms**
Clinical Features
- associated diseases: HTN, PVD, CAD, COPD, renal insufficiency
- most commonly in the abdominal aorta (50% abdominal aorta, 40% thoracic aorta, 10% ascending aorta)
- common presentation: due to acute expansion or rupture
  - syncpe
  - pain (chest, abdominal, flank, back)
  - hypotension
  - palpable pulsatile mass above the umbilicus
  - airway or esophageal obstruction, hoarseness (left recurrent laryngeal nerve paralysis), hemoptysis, or hematemesis (indicates thoracic or thoracoabdominal aortic aneurysm)
  - distal pulses may be intact
- 75% asymptomatic (discovered incidentally)
- uncommon presentations
  - ureteric obstruction and hydronephrosis (often with inflammatory aortic aneurysm)
  - gastrointestinal bleed (duodenal mucosal hemorrhage, aortoduodenal fistula)
  - aortocaval fistula
  - distal embolization (blue toe syndrome) occurs in <1% of AAAs

Investigations
- blood work: CBC, electrolytes, urea, creatinine, PTT, INR, type and cross blood
- Doppler/duplex (rule out vascular tree aneurysms elsewhere, e.g. popliteal)
- aortogram (only for EV AR)
- CT with contrast (accurate visualization, size determination, EV AR planning)
- abdominal U/S (100% sensitive, up to ±0.6 cm accuracy in size determination)
- investigations
  - common presentation: due to acute expansion or rupture
  - most commonly in the abdominal aorta (50% abdominal aorta, 40% thoracic aorta, 10% thoracoabdominal aorta)
Carotid Stenosis

Definition
• narrowing of the internal carotid artery lumen due to atherosclerotic plaque formation, usually near common carotid bifurcation into internal and external carotids

Risk Factors
• for atherosclerosis: HTN, smoking, DM, CVD or CAD, dyslipidemia

Clinical Features
• may be asymptomatic
• symptomatic stenosis may present as TIA, RIND, or stroke
• retinal insufficiency or infarct permanently or temporarily (ipsilateral amaurosis fugax), (see Ophthalmology, OP23)
• MCA contralateral occlusive symptoms

Investigations
• CBC, PTT/INR (hypercoagulable states)
• fundoscopy: cholesterol emboli in retinal vessels (Hollenhorst plaques)
• auscultation over carotid bifurcation for bruits (do not correlate with degree of stenosis)
• carotid duplex: determines severity of disease (mild/moderate/severe stenosis of occlusion)
• angiogram: “gold standard” but invasive and 1/200 risk of stroke (i.e. only used intraoperatively)
• MRA: safer than angiogram, may overestimate stenosis
• CTA

Treatment
• control of HTN, lipids, DM
• antiplatelet agents (ASA ± dipyridamole, clopidogrel) ~25% relative risk reduction
• carotid endarterectomy (generally if symptomatic and >70% stenosis)
• endovascular angioplasty ± stenting

Prognosis

Table 5. Symptomatic Carotid Stenosis: North American Symptomatic Carotid Endarterectomy Trial (NASCET)

<table>
<thead>
<tr>
<th>% Stenosis on Angiogram</th>
<th>Risk of Major Stroke or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical Rx</td>
</tr>
<tr>
<td>70-99%</td>
<td>26% over 2 yr</td>
</tr>
<tr>
<td>50-69%</td>
<td>22% over 5 yr</td>
</tr>
<tr>
<td>&lt;50%</td>
<td>Surgery has no benefit with 5% complication rate</td>
</tr>
</tbody>
</table>

Table 6. Asymptomatic Carotid Stenosis: Asymptomatic Carotid Atherosclerosis Study (ACAS) and Asymptomatic Carotid Surgery Trial (ACST)

<table>
<thead>
<tr>
<th>% Stenosis on Angiogram</th>
<th>Risk of Major Stroke or Death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medical Rx</td>
</tr>
<tr>
<td>70-99%</td>
<td>26% over 2 yr</td>
</tr>
<tr>
<td>60-99%</td>
<td>11% over 5 yr</td>
</tr>
<tr>
<td>50-69%</td>
<td>11.8% over 5 yr</td>
</tr>
</tbody>
</table>

Prevention of Disabling and Fatal Strokes by Successful Carotid Endarterectomy in Patients Without Recent Neurological Symptoms: Randomized Controlled Trial Lancet 2004;363:1491-1502
Study: Asymptomatic Carotid Surgery Trial (ACST), a RCT with follow-up at 5 yr.
Patients: 3,120 asymptomatic patients with significant carotid artery stenosis were randomized equally between immediate carotid endarterectomy (CEA) and indefinite deferral of CEA and were followed for up to 5 yr (mean 3.4 yr).
Main Outcome: Any stroke (including fatal or disabling).
Conclusions: In asymptomatic patients with significant carotid artery stenosis, immediate CEA reduced the net 5-yr stroke risk from about 12% to about 6%. Half of this 5-yr benefit involved disabling or fatal strokes.
Peripheral Venous Disease

Deep Venous Thromboembolism

- see Hematology, H35

Superficial Venous Thrombosis

Definition
- thrombosis of a superficial vein; usually spontaneous but can follow venous cannulation

Etiology
- infectious: suppurative phlebitis (complication of IV cannulation; associated with fever/chills)
- trauma
- inflammatory: varicose veins, migratory superficial thrombophlebitis, Buerger’s disease, SLE
- hematologic: polycythemia, thrombocytosis
- neoplastic: occult malignancy (especially pancreatic)
- idiopathic

Clinical Features
- most common in greater saphenous vein and its tributaries
- pain and cord-like swelling along course of involved vein
- areas of induration, erythema, and tenderness correspond to dilated and often thrombosed superficial veins
- complications
  - simultaneous DVT (up to 20% of cases), PE (rare unless DVT)
  - recurrent superficial thrombophlebitis

Investigations
- non-invasive tests (e.g. Doppler) to exclude associated DVT

Treatment
- conservative
  - moist heat, compression bandages, mild analgesic, anti-inflammatory and anti-platelet (e.g. ASA), LMWH, ambulation
- surgical excision of involved vein
  - indication: failure of conservative measures (symptoms that persist over 2 wk)
  - suppurative thrombophlebitis: broad-spectrum IV antibiotics and excision

Varicose Veins

Definition
- distention of tortuous superficial veins resulting from incompetent valves in the deep, superficial, or perforator systems

Etiology
- primary varicosities: venous valve incompetence or obstruction
  - contributing factors: increasing age, systemic hormonal contraceptive use, prolonged standing, pregnancy, obesity
- secondary varicosities: DVT, malignant pelvic tumours with venous compression, congenital anomalies, arteriovenous fistulae

Epidemiology
- primary varicose veins are the most common form of venous disorder of lower extremity
- 10-20% of population

Clinical Features (Not Correlated with Varicosity Size)
- diffuse aching, fullness/tightness, nocturnal cramping
- aggravated by prolonged standing (end of day), premenstrual
- visible long, dilated and tortuous superficial veins along thigh and leg (greater or short saphenous veins and tributaries)
- ulceration, hyperpigmentation, and induration (secondary varicosities)
• Brodie-Trendelenburg test (valvular competence test)
  - with patient supine, raise leg and compress saphenous vein at thigh, have patient stand –
    if veins fill quickly from top down then incompetent valves; use multiple tourniquets to
    localize incompetent veins

Complications
• recurrent superficial thrombophlebitis
• hemorrhage: external or subcutaneous
• ulceration, eczema, lipodermatosclerosis, and hyperpigmentation

Treatment
• largely a cosmetic problem
• conservative: elevation of leg and/or elastic compression stockings
• surgical: high ligation and stripping of the long saphenous vein and its tributaries, ultrasound-
guided foam sclerotherapy, endovenous laser therapy
• indications for surgery: symptomatic varix (pain, bleeding, recurrent thrombophlebitis), tissue
  changes (hyperpigmentation, ulceration), failure of conservative treatment, cosmetics

Prognosis
• benign course with predictable complications
• almost 100% symptomatic relief with treatment if varicosities are primary
• good cosmetic results with treatment
• significant post-operative recurrence

Chronic Venous Insufficiency

Definition
• venous insufficiency and skin damage

Etiology
• calf muscle pump dysfunction and valvular incompetence (valvular reflux) due to phlebitis,
  varicosities, or DVT
• venous obstruction

Clinical Features
• pain (most common), ankle and calf edema – relieved by foot elevation
• pruritus, brownish hyperpigmentation (hemosiderin deposits)
• stasis dermatitis, subcutaneous fibrosis if chronic (lipodermatosclerosis)
• ulceration: shallow, above medial malleolus, weeping (wet), painless, irregular outline
• signs of DVT/varicose veins/thrombophlebitis

Investigations
• Doppler U/S (most commonly used)
• venography or ambulatory venous pressure measurement (not often used)

Treatment
• conservative
  • elastic compression stockings, ambulation, periodic rest-elevation, avoid prolonged standing
  • ulcers: multilayer compression bandage, antibiotics prn
  • endovenous: laser or radiofrequency ablation, or foam sclerotherapy
• surgical
  • if conservative measures fail, or if recurrent/large ulcers
  • surgical ligation of perforators in region of ulcer (GSV/LSV ligation and stripping)
**Lymphedema**

**Definition**
- obstruction of lymphatic drainage resulting in edema with high protein content

**Etiology**
- primary
  - Milroy’s syndrome: congenital hereditary lymphedema
  - lymphedema praecox (75% of cases): starts in adolescence
  - lymphedema tarda: starts >35 yr
- secondary
  - infection: filariasis (#1 cause worldwide), post-operative
  - malignant infiltration: axillary, groin or intrapelvic
  - radiation/surgery (axillary, groin lymph node removal): #1 cause in North America

**Clinical Features**
- classically non-pitting edema
- impaired limb mobility, discomfort/pain, psychological distress

**Treatment**
- avoid limb injury (can precipitate or worsen lymphedema)
- skin hygiene
  - daily skin care with moisturizers
  - topical treatment of fungal infection; systemic treatment of bacterial infection
- external support
  - intensive: compression bandages
  - maintenance: lymphedema sleeve
- exercise
  - gentle daily exercise of affected limb, gradually increasing ROM
  - must wear a compression sleeve/bandages when doing exercises
- massage and manual lymph drainage therapy

**Prognosis**
- if left untreated becomes resistant to treatment due to subcutaneous fibrosis
- cellulitis causes rapid increase in swelling; can lead to sepsis and death
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