About this resource:

Thank you for taking the time to read the Internal Medicine Clerkship Resource. This document was created by University of Ottawa medical students for University of Ottawa medical students.

This resource was created with the purpose of being used as a reference and study guide. The content is based on faculty set objectives for this rotation and also includes references to additional resources.

How to use this resource:

This resource has been divided into sections based on the major topics covered in Internal Medicine. Please refer to the table of contents to see the breakdown of topics.

Each section covers a faculty set objective that students are expected to cover by the end of the rotation. At the end of certain sections there is a grey box title “ADDITIONAL INFORMATION.” This section provides extra details around the topic but is NOT a learning objective for the rotation.

At the end of each section is a list of references. Information from these references was used to make the handbook and can also be used as additional reading around the topics.

About the authors:

This resource was created by Kathryn Sullivan (MD2020) with help from Justine Trask (MD2021) and Isabel Shamsudeen (MD2021).

Special thank you and acknowledgment to Dr. Justine Chan for supervising and editing the resource and Dr. Lorenzo Madrazo for his past work on this document.

This is a collaborative document. We welcome suggestions for improved context and corrections of any errors. Please forward comments to: IMclerkshipresource@gmail.com

Please note that to the best of our knowledge all information and references included are up to date but errors can occur. This handbook is intended to be used by University of Ottawa students. Please do not distribute the contents of this handbook.

UNIVERSITY OF OTTAWA FACULTY OF MEDICINE
<table>
<thead>
<tr>
<th>DRUG RESISTANCE ORGANISMS</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEPHROLOGY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROACH TO ACID-BASE DISTURBANCES</td>
<td>85</td>
</tr>
<tr>
<td>APPROACH TO GLOMERULAR DISEASE</td>
<td>87</td>
</tr>
<tr>
<td>APPROACH TO HYPOKALEMIA</td>
<td>89</td>
</tr>
<tr>
<td>APPROACH TO HYPERKALEMIA</td>
<td>90</td>
</tr>
<tr>
<td>APPROACH TO HYPONATREMIA</td>
<td>91</td>
</tr>
<tr>
<td>APPROACH TO HYPERNATREMIA</td>
<td>92</td>
</tr>
<tr>
<td>APPROACH TO HYPOCALCEMIA</td>
<td>93</td>
</tr>
<tr>
<td>APPROACH TO HYPERCALCEMIA</td>
<td>94</td>
</tr>
<tr>
<td>ACUTE KIDNEY INJURY</td>
<td>95</td>
</tr>
<tr>
<td>CHRONIC KIDNEY DISEASE</td>
<td>98</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>NEUROLOGY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROACH MONONEUROPATHY AND POLYNEUROPATHY</td>
<td>100</td>
</tr>
<tr>
<td>STROKE</td>
<td>102</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>103</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ONCOLOGY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROACH TO LYMPHADENOPATHY</td>
<td>104</td>
</tr>
<tr>
<td>APPROACH TO WEIGHT LOSS</td>
<td>106</td>
</tr>
<tr>
<td>ONCOLOGICAL EMERGENCIES</td>
<td>108</td>
</tr>
<tr>
<td>MULTIPLE MYELOMA</td>
<td>110</td>
</tr>
<tr>
<td>PAIN MANAGEMENT</td>
<td>112</td>
</tr>
<tr>
<td>NAUSEA MANAGEMENT</td>
<td>113</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>113</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PHARMACOLOGY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>DESENSITIZATION THERAPY</td>
<td>114</td>
</tr>
<tr>
<td>PRE-OPERATIVE MEDICATION MANAGEMENT</td>
<td>114</td>
</tr>
<tr>
<td>CORTICOSTEROIDS</td>
<td>114</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>115</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESPIROLOGY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>PULMONARY FUNCTION TESTS</td>
<td>116</td>
</tr>
<tr>
<td>CHEST X-RAY INTERPRETATION</td>
<td>117</td>
</tr>
<tr>
<td>APPROACH TO HYPOXEMIA</td>
<td>118</td>
</tr>
<tr>
<td>APPROACH TO CHRONIC COUGH</td>
<td>120</td>
</tr>
<tr>
<td>APPROACH TO PLEURAL EFFUSION</td>
<td>122</td>
</tr>
<tr>
<td>CHRONIC OBSTRUCTIVE PULMONARY DISEASE</td>
<td>124</td>
</tr>
<tr>
<td>OBSTRUCTIVE SLEEP APNEA</td>
<td>128</td>
</tr>
<tr>
<td>PNEUMONIA</td>
<td>129</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>131</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RHEUMATOLOGY</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>APPROACH TO ARTHRITIS</td>
<td>132</td>
</tr>
<tr>
<td>RHEUMATOID ARTHRITIS</td>
<td>135</td>
</tr>
<tr>
<td>OSTEOARTHRITIS</td>
<td>136</td>
</tr>
</tbody>
</table>
SEPtic Arthritis.................................................................................. 137
CRYSTAL Arthritis ........................................................................... 138
REFERENCES.................................................................................... 139
Approach to Chest Pain

Chest pain

Cardiac
- Angina
- ACS*
- Pericarditis
- Aortic Dissection*

Pulmonary
- Pneumonia
- Parapneumonic effusion
- Pneumothorax*
- Pulmonary embolism*

GI
- Esophageal rupture*
- Esophageal spasm
- Reflux
- Cholecystitis
- Peptic ulcer disease
- Gastritis
- Pancreatitis

Other
- Herpes zoster
- Costochondritis
- Anxiety

*Potential immediate life-threatening causes of chest pain
<table>
<thead>
<tr>
<th>CARDIAC</th>
<th>DDX</th>
<th>SYMPTOMS</th>
<th>SIGNS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angina</td>
<td>Retrosternal crushing chest pressure aggravated by exertion and relieved with rest or nitro +/- nausea, SOB, CV risk factors</td>
<td>See ACS section</td>
<td>ECG, troponins</td>
<td></td>
</tr>
<tr>
<td>ACS</td>
<td>Similar symptoms to angina but duration of chest pain is greater or equal to 30 min., occurring at rest or with minimal activity</td>
<td>See ACS section</td>
<td>ECG, troponins</td>
<td></td>
</tr>
<tr>
<td>Pericarditis</td>
<td>Sharp pain radiating to the back, pleuritic, relieved by sitting forward</td>
<td>Pericardial friction rub</td>
<td>ECG- diffuse ST elevation and PR depression</td>
<td></td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>Sudden onset tearing pain that radiates to the back, mid- scapula</td>
<td>Different BP in the arms AI murmur Focal neurological deficit</td>
<td>CXR- widened mediastinum CT with contrast- dissection flap</td>
<td></td>
</tr>
<tr>
<td>PULMONARY</td>
<td>DDX</td>
<td>SYMPTOMS</td>
<td>SIGNS</td>
<td>INVESTIGATIONS</td>
</tr>
<tr>
<td>Pneumonia/parapneumonic effusion</td>
<td>Cough, fever, SOB, sputum production</td>
<td>Increased RR Crinkles on auscultation</td>
<td>CXR- pulmonary infiltrate</td>
<td></td>
</tr>
<tr>
<td>Pleuritis</td>
<td>Pleuritic chest pain, sharp quality</td>
<td>Pleuritic friction rub</td>
<td>CXR</td>
<td></td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Sudden onset unilateral sharp pleuritic chest pain, SOB</td>
<td>Unilateral decreased breath sounds Hyperresonance to percussion</td>
<td>CXR</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>Sudden onset pleuritic chest pain, S/S DVT, risk factors DVT/PE</td>
<td>Increased RR and HR Decreased O2 saturation</td>
<td>ECG CT PE</td>
<td></td>
</tr>
<tr>
<td>GI</td>
<td>DDX</td>
<td>SYMPTOMS</td>
<td>SIGNS</td>
<td>INVESTIGATIONS</td>
</tr>
<tr>
<td>Esophageal rupture</td>
<td>Severe retrosternal chest pain worse with swallowing</td>
<td>Decreased BP Palpable mediastinal air</td>
<td>CT thorax- air under the mediastinum</td>
<td></td>
</tr>
<tr>
<td>Esophageal spasm</td>
<td>Intense substernal pain with dysphagia</td>
<td>Normal exam</td>
<td>EGD</td>
<td></td>
</tr>
<tr>
<td>Reflux</td>
<td>Substernal burning, acid taste in mouth, worse with meals and lying flat, decreased with antacids</td>
<td>Usually normal may have mild erythema of the pharynx</td>
<td>EGD, manometry, pH monitoring</td>
<td></td>
</tr>
<tr>
<td>Biliary colic/cholecystitis</td>
<td>RUQ pain that is worsened with fatty meals +/- nausea and vomiting</td>
<td>Positive Murphy's sign Pain RUQ +/- jaundice</td>
<td>Abdominal US LFTs (elevated ALP, GGT)</td>
<td></td>
</tr>
<tr>
<td>PUD gastritis</td>
<td>Epigastric pain +/- hematemesis and melena</td>
<td>Epigastric tenderness</td>
<td>EGD</td>
<td></td>
</tr>
<tr>
<td>DDX</td>
<td>SYMPTOMS</td>
<td>SIGNS</td>
<td>INVESTIGATIONS</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>----------------------------------</td>
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<td>----------------</td>
<td></td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>Epigastric pain radiating to the back</td>
<td>Epigastric pain Cullen’s or grey turner sign</td>
<td>CT abdo Lipase</td>
<td></td>
</tr>
</tbody>
</table>

**OTHER**

<table>
<thead>
<tr>
<th>DDX</th>
<th>SYMPTOMS</th>
<th>SIGNS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Herpes zoster</td>
<td>Intense unilateral pain precedes dermatomal rash</td>
<td>Dermatomal rash</td>
<td>N/A</td>
</tr>
<tr>
<td>Costochondritis</td>
<td>Localized sharp or dull pain</td>
<td>Pain on palpation of chest</td>
<td>N/A</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Tightness, dyspnea, palpitations</td>
<td>Normal exam</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Approach to Syncope

- **Syncope**
  - **Neurocardiogenic**
    - Vasovagal
    - Carotid sinus hypersensitivity
    - Situational syncope
  - **Cardiovascular**
    - Verteobasilar insufficiency
    - Cerebrovascular dissection
    - Subarachnoid hemorrhage
    - Stroke/TIA
    - Migraine
  - **Neurologic**
    - Hypovolemia
    - Diuretics
    - Deconditioning
    - Autonomic neuropathy
    - Diabetes mellitus
    - Alcohol
    - Chronic kidney disease
  - **Orthostatic Hypotension**
    - Hypovolemia
    - Diuretics
    - Deconditioning
    - Autonomic neuropathy
    - Diabetes mellitus
    - Alcohol
    - Chronic kidney disease

**Mimickers of syncope**
- Neurologic – seizures, transient ischemic attack, stroke, migraine
- Metabolic – hypoglycemia, hyperventilation
- Drug-induced – alcohol and other drugs of abuse
SYNCOPE

**DEFINITION**
Sudden transient loss of consciousness and postural tone from global cerebral hypoperfusion. Consciousness returns spontaneously without intervention.

**SYMPTOMS**
- Precipitating factors and prodrome
  - **Situational syncope** – activities such as coughing, defecation, eating, laughing, urination
  - **Vasovagal syncope** – prodrome (diaphoresis, nausea, blurry vision), emotional distress, fear, prolonged standing, warm or crowded areas, abdominal pain, diaphoresis, nausea, blurred vision, lightheadedness, vertigo, slow pulse
  - **Cardiac syncope** – no prodrome, exertional syncope, unexplained falls, chest pain, dyspnea, fluttering, palpitations, slow pulse, arm exercise (subclavian steal)
  - **Carotid sinus hypersensitivity** – head movement, shaving, tight collar
  - **Orthostatic syncope** – standing after prolonged sitting, volume loss (e.g., vomiting, diarrhea, blood loss)
  - **Seizure** – aura, tonic-clonic movements, posturing
  - **Headache** – subarachnoid hemorrhage
  - **TIA/stoke** – focal neurological deficit
- Position before syncope
  - Prolonged standing – vasovagal syncope, orthostatic hypotension syncope
  - Sudden change in posture – orthostatic hypotension syncope
  - Supine – cardiac syncope
- Past medical history
  - Cardiac syncope – heart disease and CVD risk factors (diabetes, smoking, dyslipidemia, hypertension, family history of premature CVD
  - Orthostatic syncope – older age, Parkinson’s disease, autonomic neuropathy from diabetes
  - Psychiatric illness
- Family history
  - Family history of sudden cardiac death
- Medications and Allergies
  - Antiarrhythmic, antihypertensive
  - Macrolides, anti-emetics, antipsychotics, TCA (prolonged QT)

**SIGNS**
- Most patients with syncope will have a normal physical exam
- Vitals – Hypotension and bradycardia during episode, orthostatic vitals, BP in both arms, hypoxia or tachypnea if syncope due to PE or CHF
- Cardiac exam – Pathologic cardiac murmurs – aortic stenosis, hypertrophic cardiomyopathy, myxoma, Carotid sinus massage – asystole for >3 seconds or drop in SBP >50mmHg, assess for asymmetric pulses and carotid/vert/subclavian bruits
- Volume exam – Signs of hypovolemia
- Neurologic Exam – Syncope is not a neurological disease but neurological conditions may present like syncope
- Respiratory exam – cracks on inspiration in the setting of CHF

**INVESTIGATIONS**
- Bloodwork – CBC, electrolytes, glucose, BUN, Cr, bHCG – only if clinically indicated
- ECG – order for all patient with syncope
  - High risk features on ECG – persistent sinus bradycardia, 3rd degree AV block, Mobitz II 2nd degree AV block, pre-excited QRS complexes, LBBB, RBBB, VT, SVT, long or short QT, non-sustained polymorphic
**ADDITIONAL INFORMATION – SYNCOPE MANAGEMENT**

- Patients with syncope due to the life threatening causes of syncope – highlighted in red above will require thorough investigations and will need to be admitted for further treatment and testing
- In patients with an unknown cause of syncope disposition is determined based on risk stratification
  - Canadian Syncope Risk Score – see right
    - Stratify the risk of serious adverse events among patients presenting to ED with syncope, including low risk who can be discharged quickly
    - Low risk: -3 to 0
    - Medium risk: 1 to 3
    - High risk: 4 to 5
    - Very high risk: 6 to 10
  - ROSE study – admit if any of the following
    - BNP > 300, bradycardia <50, rectal exam showing fecal occult blood, anemia (Hgb<90), chest pain associated with syncope, ECG showing Q waves, saturation <95% on room air
  - The San Francisco Syncope Rule – high risk for 7 to 30 day adverse outcomes
    - CHF history, HCT <30%, ECG or cardiac monitoring abnormality, shortness of breath history, systolic blood pressure <90mmHg

VT, Brugada, ARVC
- Echocardiography – when structural heart disease is suspected
- Electrophysiology – in patients with recurrent unexplained syncope
- Exercise testing – hemodynamic and ECG abnormalities with syncope during exercise
- Neurologic testing (EEG, CT, MRI) – suspected seizures, cerebrovascular event, neurodegenerative disorder
- D-dimer or CTPA – suspected PE
Approach to Shock

- Myocardial Infarction
- Dysrhythmias
- Congestive Heart Failure
- Cardiomyopathy

- Spinal cord injury

- Sepsis
- Anaphylaxis
- Adrenal Crisis

- Hemorrhage
- Severe burns
- Dehydration
- Fistulas

- Cardiac Tamponade
- Tension
- Pneumothorax
- Pulmonary Embolism
- Aortic Stenosis
- Constrictive Pericarditis

Shock

Cardiogenic Shock

Neurogenic Shock

Distributive Shock

Hypovolemic Shock

Obstructive Shock
<table>
<thead>
<tr>
<th>SHOCK</th>
<th>DEFINITION</th>
<th>Tissue hypoxia from decreased tissue perfusion from either decreased oxygen delivery, increased oxygen consumption or inadequate oxygen utilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDIOGENIC</td>
<td>DEFINITION</td>
<td>Failure of the heart to pump adequate amount of blood to the body</td>
</tr>
<tr>
<td></td>
<td>SYMPTOMS</td>
<td>-Confusion, shortness of breath, chest pain, leg swelling, nausea, vomiting, sweating</td>
</tr>
<tr>
<td></td>
<td>SIGNS</td>
<td>-Decreased BP, orthostatic hypotension, tachycardia, tachypnea</td>
</tr>
<tr>
<td></td>
<td>INVESTIGATIONS</td>
<td>-CBC, electrolytes, BUN, Cr, liver enzymes, ABG, lactate, INR, PTT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-CXR, ECG</td>
</tr>
<tr>
<td>NEUROGENIC</td>
<td>DEFINITION</td>
<td>Interruption of sympathetic nervous system causing unopposed parasympathetic nervous system</td>
</tr>
<tr>
<td></td>
<td>SYMPTOMS</td>
<td>-Trauma or history of spinal cord injury</td>
</tr>
<tr>
<td></td>
<td>SIGNS</td>
<td>-BP&lt;90mmHg or drop of 40mmHg, bradycardia</td>
</tr>
<tr>
<td></td>
<td>INVESTIGATIONS</td>
<td>-CBC, electrolytes, BUN, Cr, liver enzymes, ABG, lactate, INR, PTT, FDP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-CT scan of the spine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-MRI if neurological deficit</td>
</tr>
<tr>
<td>DISTRIBUTIVE - Sepsis</td>
<td>DEFINITION</td>
<td>Systemic vasodilation</td>
</tr>
<tr>
<td></td>
<td>SYMPTOMS</td>
<td>-Focal infectious symptoms (meningitis, pneumonia, cellulitis, arthritis, abdominal/CVA tenderness)</td>
</tr>
<tr>
<td></td>
<td>SIGNS</td>
<td>-SIRS criteria (2 of the following): 38&lt;T&lt;36, 14&lt;WBC&lt;4, HR&gt;90, RR&gt;20 or PaCO2&lt;32</td>
</tr>
<tr>
<td></td>
<td>INVESTIGATIONS</td>
<td>-CBC, electrolytes, BUN, Cr, liver enzymes, ABG, lactate, INR, PTT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-Blood cultures, urinalysis, urine culture, wound cultures, line cultures</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-CXR</td>
</tr>
<tr>
<td>HYPOVOLEMIC</td>
<td>DEFINITION</td>
<td>Decreased intravascular volume</td>
</tr>
<tr>
<td></td>
<td>SYMPTOMS</td>
<td>-Blood loss, fluid losses or decreased PO intake</td>
</tr>
<tr>
<td></td>
<td>SIGNS</td>
<td>-Hypotension, tachycardia, tachypnea, narrow pulse pressure</td>
</tr>
<tr>
<td></td>
<td>INVESTIGATIONS</td>
<td>-CBC, electrolytes, BUN, Cr, liver enzymes, ABG, lactate, INR PTT</td>
</tr>
<tr>
<td>OBSTRUCTIVE</td>
<td>DEFINITION</td>
<td>Obstruction of blood out of the heart</td>
</tr>
<tr>
<td></td>
<td>SYMPTOMS</td>
<td>-Confusion, shortness of breath, chest pain</td>
</tr>
<tr>
<td></td>
<td>SIGNS</td>
<td>-Hypotension, tachycardia, tachypnea</td>
</tr>
<tr>
<td></td>
<td>INVESTIGATIONS</td>
<td>-CBC, electrolytes, BUN, Cr, liver enzymes, ABG, lactate, INR PTT</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-CXR, ECG</td>
</tr>
</tbody>
</table>

SVR = systemic vascular resistance, CO = cardiac output, JVP = jugular venous pressure, HR = heart rate
# ADDITIONAL INFORMATION – SHOCK MANAGEMENT

## GENERAL
1. Treatment targets for shock
   - Vitals: MAP > 65, CVP 8-12mmHg
   - Urine output > 0.5cc/kg/hr
   - Lactate <2
2. ABCs
   - Supplement O₂ +/- intubation
   - IV access with 2 large bore IVs
3. Vasopressors
   - Consider if MAP < 65, CVP <8-12mmHg and UOP < 0.5 despite 2L of IV fluids

## CARDIOGENIC
1. General management
2. IV fluid resuscitation
   - 500cc NS bolus unless in HF
3. Additional considerations for vasopressors
   - If MAP <65, CO low and SVR high can temporize with vasopressors (norepinephrine or dopamine) and consider inotropes (dobutamine)
   - If MAP ≥ 65, CO low and SVR high start inotropes (dobutamine) and if SVR remains high consider vasodilators (nitroglycerin or nitroprusside)
4. Consult cardiology/cardiac care unit

## NEUROGENIC
1. General management
2. IV fluid resuscitation
   - 1-2L crystalloid bolus
3. Additional considerations
   - Atropine for bradycardia

## DISTRIBUTIVE (sepsis)
1. General management
2. IV fluid resuscitation
   - 1-2L crystalloid bolus
3. Additional considerations
   - Rapid administration of broad spectrum antibiotics
4. Consult ICU

## HYPOVOLEMIC
1. General management
2. IV fluid resuscitation
   - 1-2L crystalloid bolus
3. Additional considerations
   - Apply pressure on external wounds and elevate
   - If continual bleeding and no response to crystalloids consider pRBC transfusion.
   - Use FFP, TXA and platelets early in bleeding (pRBC:PLT:FFP, 1:1:1)

## OBSTRUCTIVE
1. General management
2. IV fluid resuscitation
   - 500cc NS bolus unless in HF
3. Treat underlying cause
**Approach to Peripheral Edema**

**Peripheral Edema**

- **Unilateral**
  - **Acute** <72 hours
    - DVT
    - Cellulitis
    - Other: ruptured Baker’s cyst, gastrocnemius, Compartment syndrome
  - **Chronic** >72 hours
    - Venous insufficiency
    - Secondary lymphedema (tumour, radiation, surgery, infection)
    - Other: lymphoma, pelvic tumor, reflex sympathetic dystrophy

- **Bilateral**
  - **Acute** <72 hours
    - Bilateral DVT
    - Acute exacerbation of systemic chronic disease (ex. Heart failure, renal failure)
  - **Chronic** >72 hours
    - Medications*: Amlodipine, Pregabalin
    - Cardiac: CHF, constrictive pericarditis, pulmonary hypertension, OSA
    - Renal: nephrotic syndrome, CKD
    - Liver: cirrhosis
    - Lymphedema: primary vs secondary (tumor, radiation, surgery, infection)
    - Obstruction: pelvic tumor
    - Venous insufficiency
    - Low albumin: malnutrition, protein losing enteropathy
    - Leaky vessels: sepsis, pancreatitis, burns, critical illness
    - Endocrine:
      - Hyperaldosteronism,
      - ... 

**Types of Edema**
- **Venous edema**: fluid resulting from increased capillary filtration
- **Lymphedema**: fluid within skin and SC tissue resulting from lymphatic dysfunction
- **Lipedema**: form of fat maldistribution – not true edema
# ECG Interpretation

## APPROACH TO READING AN ECG

### 1. CALIBRATION
- Rectangular upward deflection at the beginning of each line
- Standard is a 10 mm deflection indicating that every 1-mm vertical box = 0.1 mV

### 2. RATE (sinus, regular, irregular)
- **If regular heart rate:** Count off each large box between two adjacent QRS complexes remembering the following sequence: 300 – 150 – 100 – 75 – 60 – 50
- **If irregular heart rate:** Count the number of QRS complexes in a 3 s interval and multiply by 20 in order to estimate the average heart rate in bpm. Or for a 10 s rhythm strip, multiply number of QRS complexes by 6.

### 3. RHYTHM

ECG shows **Sinus Rhythm** if the following are present:
- Each P wave followed by QRS
- Each QRS is preceded by a P wave
- P wave is upright in leads I and II

### 4. QRS AXIS
- Normal axis is between +90 and -30 degrees (Leads I and II upright)
- Right axis deviation – greater than +90 degrees (Lead I downward)
- Left axis deviation – more negative than -30 degrees (Lead II downward)

### 5. INTERVALS
- PR = 0.12 – 0.20 s (3-5 small boxes)
- QRS = ≤ 0.10 s (≤ 2.5 small boxes)
- QT; *corrected QT ≤ 0.44 s

## COMMON ECG ABNORMALITIES

### QRST CHANGES
- Pathologic Q waves – >30 msec or >25% height of R wave, Small q waves normal in I, aVL, V5,6, as well as isolated q wave in III, aVR, V1
- ST elevation Etiologies – Acute MI, coronary spasm, pericarditis, Takotsubo CMP, ventricular aneurysm, early repolarization
- ST depression Etiologies – Ischemia, acute true posterior MI, myopericarditis, CMP, abnormal repolarization, postpacing, hypokalemia, digoxin, core temperature disturbance, intracranial bleed
- Low voltage Etiologies – COPD, pericardial effusion, pleural effusion, elevated BMI, diffuse CAD

## CARDIAC CHAMBER ENLARGEMENT

### Right Ventricular Hypertrophy
- R>S in V1
- Right axis deviation

### Left Ventricular Hypertrophy
- S in V1 + R in V5 or V6 ≥ 35 mm OR
- R in Avl ≥11 OR
- R in lead I ≥ 15

## HEART BLOCK

### First Degree Heart Block
- PR >200ms
- 1:1 relationship between P waves and QRS complexes

### Second Degree Heart Block
- Mobitz Type I (Wenckebach)
  - PR intervals gradually increase in length before a dropped QRS
- Mobitz Type II

### Third Degree Heart Block
- Complete failure of conduction between the atria and the ventricles
- Sudden intermittent loss of AV conduction (dropped QRS) without preceding lengthening of PR interval
- More likely to progress to 3rd degree block

<table>
<thead>
<tr>
<th>MYOCARDIAL ISCHEMIA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Transient Ischemia</strong></td>
</tr>
<tr>
<td>- Commonly seen as reversible depression of the ST segment and/or inversion of the T wave</td>
</tr>
<tr>
<td><strong>STEMI</strong></td>
</tr>
<tr>
<td>- ST-segment elevation in certain leads implicate ischemic damage to certain regions of the myocardium</td>
</tr>
<tr>
<td>✓ Anteroseptal: V1 and V2</td>
</tr>
<tr>
<td>✓ Anteroapical: V2 and V4</td>
</tr>
<tr>
<td>✓ Anterolateral: I, aVL, V5, V6</td>
</tr>
<tr>
<td>✓ Inferior: II, III, AvF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PERICARDITIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Diffuse ST-segment elevation in most leads, usually sparing aVR and V1; PR-segment depression in several leads</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ELECTROLYTE ABNORMALITIES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperkalemia</strong></td>
</tr>
<tr>
<td>- Tall peaked T waves</td>
</tr>
<tr>
<td>- Flattened P waves</td>
</tr>
<tr>
<td>- Widened QRS</td>
</tr>
<tr>
<td><strong>Hypokalemia</strong></td>
</tr>
<tr>
<td>- ST depression and flattened T waves</td>
</tr>
<tr>
<td>- Prominent U wave</td>
</tr>
</tbody>
</table>
Secondary Hypertension

- Renal
  - Renal parenchymal disease
  - Renal vascular disease (atherosclerosis, fibromuscular)

- Endocrine
  - Hyperaldosteronism
  - Pheochromocytoma
  - Cushing’s disease
  - Thyroid disease
  - Hypercalcemia

- Drugs
  - Oral contraceptive pills
  - Steroids
  - NSAIDs
  - Cocaine
  - Alcohol
  - Epo
  - Cyclosporine

- Other
  - Aortic coarctation
  - OSA
  - Polycythemia Vera
# SECONDARY HYPERTENSION

## DEFINITION

Blood pressure > 140/90. Consider in patients with hypertension under the age of 30, sudden onset hypertension, or severe refractory hypertension.

## RENAL

<table>
<thead>
<tr>
<th>DDX</th>
<th>SYMPTOMS</th>
<th>SIGNS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal parenchymal</td>
<td>-May be consistent with symptoms of diabetes, PCOS, glomerulonephritis</td>
<td>-Unremarkable +/- palpable kidneys in PCOS, edema</td>
<td>-Cr, urinalysis, ACR/PCR for albuminuria</td>
</tr>
<tr>
<td>Renal vascular (atherosclerosis, FMD, scleroderma)</td>
<td>-May have acute renal failure associated with ACEI/ARB use -Shortness of breath</td>
<td>-Peripheral edema -Crackles on auscultation -Renal bruit</td>
<td>-MRA, CTA, duplex US, angio, plasma renin</td>
</tr>
</tbody>
</table>

## ENDOCRINE

<table>
<thead>
<tr>
<th>DDX</th>
<th>SYMPTOMS</th>
<th>SIGNS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperaldosteronism – renin independent increase in aldosterone (ex. Conn’s syndrome)</td>
<td>-Headache, muscle weakness, polyuria, polydipsia</td>
<td>-No peripheral edema</td>
<td>-Hypokalemia, metabolic alkalosis, mild hypernatremia -AM plasma renin and aldosterone</td>
</tr>
<tr>
<td>Cushing’s disease – cortisol excess due to ACTH-secreting pituitary adenoma, adrenal tumor, ectopic ACTH</td>
<td>-History of DM, obesity -Acne, hirsutism -Depression, insomnia, psychosis, impaired cognition</td>
<td>-Central obesity, dorsocervical fat pad, bruising, round facies, facial plethora, purple striae -Proximal myopathy</td>
<td>-24 hr urinary free cortisol -Overnight 1mg dexamethasone suppression test -Salivary cortisol</td>
</tr>
<tr>
<td>Pheochromocytoma – metanephrines secreting adrenal tumour and can be extra-adrenal</td>
<td>-Pain: headache, chest -Paroxysms of palpitations and perspiration -Pallor -Weight loss</td>
<td>-Paroxysmal HTN -Tachycardia -Fever</td>
<td>-24hr urinary fractionated metanephrines -Plasma free metanephrines -Adrenal CT -Can consider genetic workup</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>-Signs and symptoms of hyper or hypothyroidism</td>
<td>-Elevated dBP in hypothyroidism -Elevated sBP in hyperthyroidism</td>
<td>Thyroid function tests</td>
</tr>
</tbody>
</table>

## OTHER

<table>
<thead>
<tr>
<th>DDX</th>
<th>SYMPTOMS</th>
<th>SIGNS</th>
<th>INVESTIGATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aortic coarctation</td>
<td>-Asymptomatic +/- chest pain, SOB, syncope</td>
<td>-Decreased lower extremity pulses -Systolic murmur -Radial-femoral delay</td>
<td>-TTE -CXR</td>
</tr>
<tr>
<td>Obstructive sleep apnea</td>
<td>-Snoring, choking/cessation of breathing at night</td>
<td>-Obesity -May have enlarged tonsils or adenoids</td>
<td>-Overnight polysomnography</td>
</tr>
</tbody>
</table>
| Polycythemia Vera  
-elevated RBC mass | -Morning headaches, daytime fatigue  
-Impaired concentration | - Increased neck circumference | - Headache, dizziness, tinnitus, blurred vision  
- Transient visual disturbances  
- Burning and erythema of extremities  
- Pruritus  
- Plethora  
- Splenomegaly  
- Engorged retinal veins | - HCT>49% in men  
- HCT>48% in women  
- Low EPO level  
- JAK2 mutation |
**Hypertensive Emergency**

### DEFINITION
- Hypertensive emergency: severe hypertension with acute end-organ damage including cerebrovascular damage (hypertensive encephalopathy, stroke, papilledema), cardiovascular damage (CHF, ACS, aortic dissection), renal damage (proteinuria, hematuria, AKI), and hematological consequences (Microangiopathic hemolytic anemia)
- Hypertensive urgency: sBP>180 or dBP>110 with minimal or no end-organ damage

### SYMPTOMS
- Cerebrovascular damage → Headache, vision changes, confusion, symptoms of stroke
- Cardiovascular damage → Chest pain, back pain, shortness of breath, leg swelling
- Renal damage → Nocturia, leg swelling, oliguria

### SIGNS
- Cerebrovascular damage → Altered LOC, papilledema, signs of stroke
- Cardiovascular damage → New murmur, peripheral edema, elevated JVP, crackles in lung fields, S3, S4
- Renal damage → Peripheral edema, oliguria, anuria

### INVESTIGATIONS
- CBC, electrolytes, BUN, Cr
- Blood smear detect microangiopathic hemolytic anemia
- Urinalysis
- CXR, ECG, troponins and CK
- CT head if neurological findings

### MANAGEMENT

#### HYPERTENSIVE EMERGENCY
- **ABC**- supplemental oxygen, IV access, cardiac and respiratory monitoring
- Lower BP within minutes. Decrease MAP by 25% in the first 1-2 hours.
- **IV** antihypertensive therapy: labetalol, nitroglycerin, nitroprusside, hydralazine
- **Special considerations**
  - Ischemic stroke → do not decrease BP unless BP >220/120 or lysis planned
  - Aortic dissection → STAT rapid reduction in BP (sBP to 110-120) with Labetolol
  - Excess catecholamines → avoid treatment with BB
  - ACS → use nitrates

#### HYPERTENSIVE URGENCY
- Rule out hypertensive emergency
- Treatment initiated with aim to lower BP within hours. Close follow up recommended in 48 – 72 hours.
- **PO** antihypertensive therapy: captopril, labetalol, clonidine, hydralazine
<table>
<thead>
<tr>
<th>ADDITIONAL INFORMATION – DRUGS FOR HYPERTENSIVE CRISES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HYPERTENSIVE EMERGENCY</strong></td>
</tr>
<tr>
<td>Nitroprusside 0.25 – 10 ug/kg/min IV</td>
</tr>
<tr>
<td>Nitroglycerin 5 – 1000 ug/min IV</td>
</tr>
<tr>
<td>Labetolol 20 – 80 mg IV q10 min or 0.5 – 2mg/min IV</td>
</tr>
<tr>
<td>Hydralazine 10 – 20 mg q20-30 min IV</td>
</tr>
<tr>
<td>Phentolamine 5-15 mg bolus q5 min IV</td>
</tr>
<tr>
<td><strong>HYPERTENSIVE URGENCY</strong></td>
</tr>
<tr>
<td>Captopril 12.5 – 100 mg PO</td>
</tr>
<tr>
<td>Clonidine 0.1 – 0.2 mg PO</td>
</tr>
<tr>
<td>Labetolol 200-800 mg PO</td>
</tr>
<tr>
<td>Hydralazine 10 – 60 mg PO</td>
</tr>
</tbody>
</table>
# Acute Coronary Syndrome

## Definition

**Acute Coronary Syndrome**

- Disruption of atherosclerotic plaque in coronary artery > platelet aggregation > intracoronary thrombus. The spectrum of ACS that results depends on the degree of coronary obstruction and associated ischemia.

## Unstable Angina

- Acceleration of ischemic symptoms – angina that is new onset, crescendo or at rest
- No ST elevation on ECG + negative troponins

## NSTEMI

- Acute myocardial infarction – an ischemic syndrome leading to irreversible myocardial necrosis
- No ST elevation on ECG + elevated troponins

## STEMI

- Acute myocardial infarction – an ischemic syndrome leading to irreversible myocardial necrosis
- ST elevation on ECG + elevated troponins

## Symptoms

- Typical angina: retrosternal pressure, radiation to neck, jaw, arms and precipitated by exertion, relieved by rest or nitroglycerin
- Atypical symptoms: in elderly, women, diabetics, inferior ischemia
- In ACS: new-onset, crescendo or at rest

## Signs

- Signs of ischemia: S4, new MR murmur with papillary muscle dysfunction
- Signs of heart failure: elevated JVP, S3, crackles in lung fields

## Investigations

- ECG: monitor for dynamic changes, repeat with any change of symptoms and at 6-12 hours
- Cardiac biomarkers (troponins): 2-6 hours after symptom onset and repeat 6 hours later
- If low risk → stress test or if high risk → coronary angiogram

## Management

### General

- Stabilize: ABCs (O2, IV access, cardiac monitors, pulse oximetry)
- ASA 325mg
- Nitroglycerin 0.3mg SL q5minX3 → **Counterindications**: Inferior STEMI, hypotension, phosphodiesterase inhibitor use
- Morphine IV
- B-blockers → **Counterindications**: heart failure, risk of cardiogenic shock, heart block, asthma, low output state

### NSTEMI

- Calculate TIMI score for risk stratification → TIMI: Age ≥65, ≥3 CAD risk factors, known CAD (stenosis >50%), ASA use within 7 days, ≥2 angina episodes within 24 h, increased cardiac markers, ST deviation ≥0.5 mm
- Anti-platlet: Ticagrelor or clopidogrel. Consider GIIb/IIIa inhibitor if plans for PCI.
- Anticoagulation: if TIMI ≥3 consider early LMWH and angiography. If plans for PCI UFH. PCI
- Coronary angiography with revascularization (PCI or CABG) if high risk

### STEMI

- PCI: preferred reperfusion method if within 12 hours of symptom onset and within 90 min. of presentation
- Thrombolysis: indicated if within 12 hours of symptom onset, PCI not available within 90 min.
### COUNTERINDICATIONS THROMBOLYSIS
- prior ICH, known structural CV lesion, known malignant IC neoplasm,
- significant closed-head or facial trauma ≤3 mo, ischemic stroke ≤3 mo, active bleeding, suspected aortic dissection

### POST-ACS
- Risk factor and lifestyle modifications (BP, cholesterol, diabetes, exercise, fat reduction, smoking cessation)
- Anti-platlet/anti-coagulation: ASA 81mg+ticagrelor (at least 1 mo, if stent 1 yr). Warfarin x3mo if high risk.
- Nitroglycerin: symptomatic relief of ischemia symptoms
- β-blockers: metoprolol, atenolol or bisoprolol
- Calcium channel blockers: NOT recommended 1st line but as alternative to BB.
- ACEi: Ramipril can prevent ventricular remodeling
- HMG CoA inhibitors: simvastatin, atorvastatin
### Congestive Heart Failure

#### Congestive Heart Failure

**Definition**
- When the heart is unable to pump blood forward at a sufficient rate to meet the metabolic demands of the body or is able to do so only if cardiac filling pressures are abnormally high
- The final and most severe manifestation of nearly every form of cardiac disease (coronary atherosclerosis, myocardial infarction, valvular disease, hypertension, congenital heart disease and cardiomyopathies)

#### Pathophysiology

- **Cardiac Insult**
  - Ischemic heart disease, hypertension, valvular disease

- **Systolic Dysfunction**
  - Inability of ventricles to expel sufficient blood to the body

- **Diastolic Dysfunction**
  - Failure of ventricle to relax and fill properly

- **Neurohormonal System Activation**
  - Sympathetic nervous system, renin-angiotensin system, antidiuretic hormone

- **Compensation**
  - ↑ heart rate
  - ↑ ventricular contractility
  - ↑ cardiac output

- ** Decompensation**
  - Symptomatic heart failure

#### Symptoms

- Low cardiac output → fatigue, weakness, exercise intolerance, syncope, change in mental status
- Left-Sided HF Congestion → dyspnea, orthopnea, paroxysmal nocturnal dyspnea
- Right-Sided HF Congestion → peripheral edema, abdominal distension, RUQ discomfort
- Functional Classification (New York Heart Association)
  - **Class I**: symptomatic only with greater than ordinary activity
  - **Class II**: symptomatic with ordinary activity
  - **Class III**: symptomatic with minimal activity
  - **Class IV**: symptomatic at rest

#### Signs
- Low cardiac output → narrow pulse pressures, hypotension, cool extremities, mottling, low cap refill, peripheral cyanosis
- Left-Sided HF Congestion→ respiratory crackles and decreased air entry, mitral regurgitation, S3
- Right-Sided HF Congestion→ elevated JVP, hepatomegaly, ascites, jaundice, peripheral edema, tricuspid regurgitation, S3

INVESTIGATIONS
- Precipitating factors (FAILURE): Forgot to take medications, Anemia/Arrhythmia, Ischemia/Infection, Lifestyle (salt intake), Up regulators (TSH, HTN, tachycardia), Rheumatic (valvular disease), Embolism
- Bloodwork: ↑ creatinine/BUN, ↓ Na, ↑ LFTs, ↑ BNP
- CXR: pulmonary edema (Kerley B lines, bronchio-alveolar cuffing), pleural effusions, cardiomegaly
- ECG: evidence of ischemia
- Echocardiogram: EF helps to distinguish between systolic and diastolic dysfunction, assess for wall motion abnormalities in ischemia, assess for valvular disease, pericardial abnormalities and infiltrative disease
- Coronary angiography: required to rule out ischemia

MANAGEMENT
 ACUTE DECOMPENSATED HEART FAILURE
- Lasix: give IV, general rule of thumb to give double home dose and give IV
- Morphine: decrease anxiety and preload
- Nitrates: caution in patients with pre-load dependent right HF
- Oxygen and non-invasive ventilation: CPAP/BiPAP decreases preload
- Position: patient sitting up with legs down
- If patient shows signs of severe decompensation (hypotension, congestion, cool extremities) ionotropes (ex. dopamine, dobutamine or phosphodiesterase inhibitors) required

CHRONIC HEART FAILURE WITH REDUCED EJECTION FRACTION
- Treat underlying cause
- Education: salt restriction, fluid restriction (if hypoNa), exercise training in ambulatory patients
- Medications with mortality benefit in patients with systolic dysfunction: titrate up to heart failure doses!
  - ACEI or ARB
  - Hydralazine + nitrates (for those who cannot tolerate ACEI/ARB or blacks with Class III/IV)
  - Beta-blocker
  - Aldosterone antagonist (for Class II/IV and EF<35%, watch K!)
  - Neprilysin inhibitor + ARB (if start, discontinue ACEI)
- Medications for symptoms:
  - Diuretics (for volume overload)
  - Digoxin (decrease in hospitalizations)
- Devices:
  - CRT/Biventricular pacing (EF <35%, LBBB and QRS >130 ms)
  - ICD (EF<35%, Pts with MI + EF<30%)

ADDITIONAL INFORMATION – CARDIOMYOPATHY

DILATED CARDIOMYOPATHY
- Ventricular dilatation and decreased contractility in the absence of myocardial disease caused by ischemia/infarct, valvular disease or hypertension
- Etiologies: familial, idiopathic, infectious, toxic, infiltrative, autoimmune, stress-induced, arrhythmogenic right ventricular cardiomyopathy, tachycardia, metabolic
| HYPERPROPHIC CARDIOMYOPATHY | • Hypertrophy disproportionate to hemodynamic load  
• 50% sporadic, 50% familial  
• Autosomal dominant mutations in cardiac sarcomere genes > myocardial fiber disarray with hypertrophy |
|-----------------------------|--------------------------------------------------------------------------------------------------|
| RESTRICTIVE CARDIOMYOPATHY  | • Impaired ventricular filling with decreased compliance in non-hypertrophied, non-dilated ventricles  
• Etiologies: Autoimmune (scleroderma, polymyositis/dermatomyositis), amyloidosis, sarcoidosis, hemochromatosis |
ATRIAL FIBRILLATION

DEFINITION
- Irregular rhythm characterized by a fast atrial rate such that P waves are not discernible on ECG
- Afib leads to blood stasis in the atrium which promotes clot formation and increases risk for stroke/TIA. It can also decrease cardiac output precipitating heart failure.

CLASSIFICATION
- Paroxysmal: atrial fibrillation episode terminates spontaneously
- Permanent/chronic: continuous atrial fibrillation unresponsive to cardioversion
- Persistent: atrial fibrillation sustained for 7 days or only terminates with cardioversion
- Lone: atrial fibrillation in individuals <60yo, with no structural heart disease or risk factors

ETIOLOGY
- Cardiovascular: HTN, CAD, cardiomyopathy, myocarditis, infiltration (amyloid, sarcoid), valve disease, arrhythmia, pericarditis, surgery
- Pulmonary: COPD, pulmonary embolism, pleural effusion
- Metabolic: obesity, thyrotoxicosis
- Drugs: theophylline, adenosine, digitalis, beta agonists, alcohol
- Idiopathic

SYMPTOMS
- Palpitations, chest pain, dyspnea, dizziness, syncope
- Past medical history→ AF, SVT, WPW, CAD, HF, hypertension, diabetes, stroke, TIA, thyroid dysfunction
- DVT/PE risk factors

SIGNS
- Heart rate→ tachycardia, rhythm→ irregularly irregular
- Hypotension if unstable
- Complications of afib→ signs of CHF exacerbation or stroke/TIA

INVESTIGATIONS
- ECG: no organized P waves and chaotic fibrillatory baseline, rate irregularly irregular with narrow QRS
- Bloodwork: K, Mg, thyroid function tests
- CXR, echocardiogram

MANAGEMENT

STROKE RISK STRATIFICATION – CHA2DS2-VASc

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Points</th>
<th>CHADS2</th>
<th>Stroke Risk (%/Yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
<td>2</td>
<td>2.2</td>
</tr>
<tr>
<td>Age&gt;75</td>
<td>2</td>
<td>3</td>
<td>3.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Prior stroke/TIA</td>
<td>2</td>
<td>5</td>
<td>6.7</td>
</tr>
<tr>
<td>Vascular Disease</td>
<td>1</td>
<td>6</td>
<td>9.8</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
<td>7</td>
<td>9.6</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>8</td>
<td>6.7</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>15.2</td>
<td></td>
</tr>
</tbody>
</table>

**TREATMENT**

- **Rate control**: B-blocker, diltiazem, verapamil
- **Anticoagulation**
  - Age<65 and CHADS₂ 0 → ASA 81mg
  - Age>65 and CHADS₂ ≥1 → NOACs (ex. Apixaban, dabigatran, rivaroxaban) or warfarin
- **Cardioversion**
  - Unstable patients (hypotension, angina, uncontrolled heart failure) cardiovert STAT
  - Afib<24-48h can cardiovert without anticoagulation
  - Afib>24-48h anticoagulation required 3 weeks prior and 4 weeks after cardioversion
- **Antiarrhythmic drugs**
  - Initiate if bothersome symptoms or episodes of prolonged afib in which symptoms do not resolve with rate control
  - Propafenone, flecainide → patients with no or minimal heart disease
  - Amiodarone → patients with LV dysfunction or CAD

**ADDITIONAL INFORMATION – PHARMACOLOGY OF ANTIARRHYTHMIC MEDICATIONS**

| CLASS IA | Moderate block (↓↓phase 0 upstroke rate; prolonged action potential)  
| e.g. Quinidine, Procainamide, Disopyramide |
| CLASS IB | Mild block (↓phase 0 upstroke rate; shortened action potential)  
| e.g. Lidocaine, Mexiletine |
| CLASS IC | Marked block (↓↓↓ phase 0 upstroke rate; no change in action potential)  
| e.g. Flecainide, Propafenone |
| CLASS II | β-adrenergic receptor blockade  
| e.g. Propanolol, Esmolol, Metoprolol |
| CLASS III | K+ channel blockade  
| e.g. Amiodarone, Dronedarone, Sotalol, Ibutilide, Dofetilide |
| CLASS IV | Ca++ channel antagonists  
| e.g. Verapamil, Diltiazem |
References
Endocrinology

Approach to Hypoglycemia

Hypoglycemia

No DM present

- Increased insulin
  - Exogenous insulin
  - Insulinoma
  - Anti-insulin antibodies
  - Sulfonylureas

- Decreased glucose production

- Increased IGF-II

- Non-islet tumour

Other

- DM medication
- Missed meals
- Renal failure

- Postprandial
  - Excessive response to glucose load

DM present

- Increased IGF-II

- Decreased glucose production

- Hypoglucoma
  - Adrenal insufficiency
  - Glucagon deficiency
  - Hepatic failure
  - Renal failure
  - CHF

- Exogenous insulin
  - Anti-insulin antibodies
  - Sulfonylureas
**HYPOGLYCEMIA**

**DEFINITIONS**
- Hypoglycemia is blood glucose < 4.0 mmol/L and tends to occur in patients with DM receiving insulin or oral antihyperglycemia agents (insulin secretagogues)
- Hypoglycemia is clinically defined by Whipple’s Triad
  - Serum glucose <2.5 mmol/L in males and <2.2 mmol/L in females
  - Symptoms of hypoglycemia
  - Rapid relief provided by glucose administration

**SYMPTOMS**
- Adrenergic symptoms – caused by autonomic nervous system activity
  - Palpitations, sweating, anxiety, tremor, tachycardia
- Neuroglycopenic symptoms – caused by decreased CNS activity
  - Dizziness, headache, clouding vision, mental dullness, weakness, confusion, seizures, coma

**SIGNS**
- Vitals – tachycardia
- Change in mental status – somnolence, stupor, coma if severe

**INVESTIGATIONS**
- Bloodwork – CBC w/ differential, electrolytes, Cr, BUN, LFTs, TSH, albumin, IGF-1/IGF-II ratio when appropriate
- 72 hour fast with monitored blood glucose
- At time of hypoglycemia: C-peptide, B-OH-butyrate and sulfonylurea levels
  - C-peptide can be increased with insulinoma and sulfonylurea use and decreased with exogenous insulin

**MANAGEMENT**
- If severe – ABCs and IV access
- For patients who can tolerate po – 25-50g of either glucose tablets, paste, fruit juice
- For patients who cannot tolerate po – 25-50g D50 IV or 0.5-1mg glucagon IM/SC
# Diabetes

## Definitions

- **Type I Diabetes Mellitus**
  - Autoimmune condition causing beta islet cell destruction in the pancreas - causes absolute insulin deficiency - Ketosis
  - Onset usually in childhood but can occur throughout adulthood
  - Associated with Anti-GAD, Anti-islet cell, Anti-insulin antibodies

- **Type II Diabetes Mellitus**
  - Characterized by insulin resistance and relative insulin deficiency
  - Onset generally later in life
  - Associated with obesity and metabolic syndrome

- **Mature-Onset Diabetes of the Young**
  - Autosomal dominant forms of DM due to defects in insulin secretion genes

- **Secondary causes of diabetes**
  - Exogenous glucocorticoids, glucagonoma, pancreatic (pancreatitis, hemochromatosis, cystic fibrosis), endocrinopathies (Cushing’s acromegaly), gestational, drugs (protease inhibitors, atypical antipsychotics)

## Diagnostic Criteria

- Fasting plasma glucose ≥ 7.0 mmol/L OR
  - A1C ≥ 6.5%
  - 2hPG in a 75g oral glucose tolerance test (OGTT) ≥ 11.1 mmol/L OR
  - Random plasma glucose ≥ 11.1 mmol/L

- Asymptomatic hyperglycemia + 1 test in DM range – repeat test for confirmation of diagnosis

- Symptomatic hyperglycemia + 1 test in DM range – diagnose with DM

## Symptoms

- Can be asymptomatic, especially T2DM
- Symptoms of hyperglycemia – polydipsia, polyphagia, polyuria, weight loss, blurry vision

## Signs

- HEENT – fundoscopy and thyroid exam
- Cardiovascular – signs of peripheral vascular disease, bruits
- Foot exam – sensation (monofilament test), ulcers or infections
- Neurological exam – assess for peripheral neuropathy and mononeuropathy

## Complications of Diabetes

- Macrovascular complications, microvascular complications, increased risk of infections – UTI, osteomyelitis, candidiasis, mucormycosis, necrotizing external otitis

## Macrovascular

- Coronary artery disease
- Peripheral arterial disease – lower extremity claudication, intestinal angina, foot ulceration
- Ischemic stroke

## Microvascular

- Retinopathy
  - Non-proliferative – dot & blot retinal hemorrhages, cotton-wool/protein exudates
  - Proliferative – neovascularization, vitreous hemorrhage, retinal detachment, blindness
- Nephropathy
- Diffuse thickening of glomerular basement membrane leading to microalbuminuria → proteinuria → nephrotic syndrome → renal failure

**Neuropathy**
- Peripheral – symmetric distal sensory loss, paraesthesias
- Autonomic – gastroparesis, constipation, neurogenic bladder, erectile dysfunction, postural hypotension
- Mononeuropathy – sudden-onset central or peripheral deficit

**INVESTIGATIONS**

- Diagnostic tests as above
- Baseline investigations
  - Bloodwork - HbA1c, fasting lipids, Cr
  - Microalbumin:creatinine ratio
  - ECG
- HbA1c q3mo
- Annual fasting lipid profile, ACR, eGFR and eye exam

**MANAGEMENT**

**OUTPATIENT MANAGEMENT**

- Treatment goals – HbA1C ≤ 7.0%, FPG or pre-prandial PG 4.0 – 7.0 mmol/L, 2hr PPG 5.0 – 10.0 mmol/L
  - A1C > 7% associated with increased risk of microvascular and macrovascular complications
- Lifestyle modifications – weight loss, Canadian Food Guide, exercise
- Medications – see below

**INPATIENT MANAGEMENT**

- Treatment Goals – avoid hypoglycemia and extreme hyperglycemia
- Identify reversible causes and exacerbating factors – dextrose, IV fluids, glucocorticoids
- Monitor – BG fingersticks (fasting, qAC, qHS), HbA1C
- Consider modifications to outpatient treatment regimen
  - In T1DM never stop basal insulin as can cause DKA
  - In T2DM can stop oral diabetes medications to avoid hypoglycemia or medication interactions unless short hospital stay, good outpatient control, no IV contrast, normal diet, consider reduction of long acting insulin by 30-50% if not eating
  - Discharge medications – same as admission unless poor outpatient control
## Diabetes Medications

### ORAL HYPOGLYCEMIC AGENTS

<table>
<thead>
<tr>
<th>Class</th>
<th>Mechanism of Action</th>
<th>Decrease in A1C</th>
<th>Other considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biguanides</td>
<td>Lower hepatic gluconeogenesis</td>
<td>1.5%</td>
<td>• First line – Improved cardiovascular outcomes&lt;br&gt;• Weight neutral&lt;br&gt;• No hypoglycemia&lt;br&gt;• GI S/E&lt;br&gt;• CONTRAINDICATIONS – renal or liver failure</td>
</tr>
<tr>
<td>Metformin</td>
<td>Inhibits pancreatic alpha-amylase and intestinal alpha-glucosidase -&gt; delays intestinal glucose absorption</td>
<td>0.5 – 0.8%</td>
<td>• Not recommended as initial therapy in those with marked hyperglycemia&lt;br&gt;• Weight neutral&lt;br&gt;• No hypoglycemia&lt;br&gt;• GI S/E</td>
</tr>
<tr>
<td>Alpha-glucosidase</td>
<td>Enhances insulin sensitivity in peripheral tissues and liver</td>
<td>1.0%</td>
<td>• Weight gain&lt;br&gt;• No hypoglycemia&lt;br&gt;• S/E (many and severe) – hepatotoxicity, CHF, edema, bone fractures, increased risk of MI&lt;br&gt;• CONTRAINDICATIONS – liver disease, CHF NYHA III and IV</td>
</tr>
<tr>
<td>inhibitor</td>
<td>Activates sulfonylurea receptor on beta cell to stimulate endogenous insulin production</td>
<td>1.5%</td>
<td>• Relatively rapid blood glucose-lowering response&lt;br&gt;• Weight gain&lt;br&gt;• Hypoglycemia risk&lt;br&gt;• Consider using other classes first in patients who are at high risk for hypoglycemia</td>
</tr>
<tr>
<td>Acarbose</td>
<td>Same as sulfonylureas</td>
<td>1.5%</td>
<td>• Shorter duration of action than sulfonylureas -&gt; lowered risk of hypoglycemia&lt;br&gt;• Weight gain</td>
</tr>
<tr>
<td>Thiazolidinediones</td>
<td>Amplifies incretin pathway by blocking degradation of GLP-1 and GIP increasing insulin secretion</td>
<td>0.5%</td>
<td>• Improved postprandial control&lt;br&gt;• Rare increased risk of CHF&lt;br&gt;• Weight neutral&lt;br&gt;• No hypoglycemia</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>Actives incretin pathway</td>
<td>0.5%</td>
<td>• Decreased CV events&lt;br&gt;• Improved postprandial control&lt;br&gt;• Weight loss&lt;br&gt;• No hypoglycemia&lt;br&gt;• Parenteral administration&lt;br&gt;• GI S/E&lt;br&gt;• CONTRAINDICATIONS – FMHx of medullary thyroid cancer or MEN2</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td>Glucose and dose dependent insulin secretion increase</td>
<td></td>
<td>• Decreased CV deaths, HF and slows progression of kidney disease&lt;br&gt;• Risk of normoglycemic DKA&lt;br&gt;• Weight loss&lt;br&gt;• S/E – Increased risk of fungal GU infections, hypovolemia, increased LDL</td>
</tr>
</tbody>
</table>

- **SGLT-2 Inhibitors**
  - Canagliflozin
  - Dapagliflozin
  - Empagliflozin

- **GLP-1 receptor agonist**
  - Exenatide
  - Liraglutide

- **DPP-4 Inhibitor**
  - Sitagliptin
  - Linagliptin

- **Meglitinides**
  - Nateglinide
  - Repaglinide
<table>
<thead>
<tr>
<th>Insulin Type</th>
<th>Preparation</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PRANDIAL (BOLUS)</td>
<td>Rapid-acting NovoRapid, Fiasp, Humalog, Apidra</td>
<td>10-15 min</td>
<td>60-90 min</td>
<td>3-5 h</td>
<td>Taken before meal</td>
</tr>
<tr>
<td></td>
<td>Short-acting Humulin R, Novolin Toronto</td>
<td>30 min</td>
<td>2-3 h</td>
<td>5-8 h</td>
<td>Taken ~30 minutes before meal</td>
</tr>
<tr>
<td>BASAL</td>
<td>Intermediate-acting NPH, Humulin N</td>
<td>1-3 h</td>
<td>5-8 h</td>
<td>12-18 h</td>
<td>Often BID</td>
</tr>
<tr>
<td></td>
<td>Long-acting Lantus, Levemir, Toujeo</td>
<td>2 h</td>
<td>No peak</td>
<td>20-24 h</td>
<td>Once daily</td>
</tr>
</tbody>
</table>
**Diabetic Ketoacidosis**

<table>
<thead>
<tr>
<th>DIABETES KETOACIDOSIS (DKA)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATHOPHYSIOLOGY</strong></td>
</tr>
<tr>
<td>• DKA occurs in the setting of decreased insulin and increased glucagon</td>
</tr>
<tr>
<td>• Occurs in T1DM (and ketosis-prone T2DM)</td>
</tr>
<tr>
<td>• Increased gluconeogenesis, increased glycogenolysis and decreased glucose uptake</td>
</tr>
<tr>
<td>• Ketosis due to the oxidation of fatty acids and decreased ketone clearance</td>
</tr>
</tbody>
</table>

**PRECIPITANTS — “Is”**

- Insulin deficiency, Initial diagnosis, Latrogenesis (glucocorticoids; SGLT2 inhibitors), Infection, Inflammation (pancreatitis, cholecystitis), Ischemia or Infarction (MI, Stroke, Gut), Intoxication (alcohol, drugs)

**SYMPTOMS**

- Hyperglycemia – polyuria, polydipsia and dehydration
- Nausea, vomiting, abdominal pain, ileus

**SIGNS**

- General – tachycardia, hypotension, acetone breath
- Change in mental status – somnolence, stupor, coma
- Dehydration – dry mucous membranes, decreased skin turgor
- Kussmaul’s breathing – compensate for metabolic acidosis

**INVESTIGATIONS**

- Bloodwork – CBC w/ differential, electrolytes, VBG, Ca, Mg, PO₄, Cr, BUN, glucose, beta hydroxy butarate, serum osmolality, LFTs, urinalysis, troponins, lipase, bHCG in females of childbearing age
- ECG – MI possible precipitant and electrolyte abnormalities can cause ECG changes

**MANAGEMENT**

- DKA is a diabetic emergency begin treatment ASAP
- Goal is to resolve anion gap metabolic acidosis
  1. ABC, O₂, IV access
  2. Rule out possible precipitant
  3. Aggressive rehydration
    a. 1L/h NS in the first hour. Tailor rehydration to degree of dehydration and CV status.
    b. Monitor urine output
  4. Insulin therapy
    a. IV Insulin 0.1 U/kg/h
    b. Continue insulin until anion gap is normal. If AG still high, do NOT discontinue insulin infusion. If blood glucose <8 start dextrose infusion.
    c. Glucose scans q1h
  5. Electrolyte repletion – K, PO₄, HCO₃
    a. If serum K < 3.3 mmol/L, start insulin AFTER K is replaced 40mEq/L K. When K 3.5-4.5 mmol/L add KCl 20-40mEq/L to IV fluid
    b. HCO₃ repletion if pH <7 or if cardiac instability
    c. PO₄ repletion if PO₄ <1
    d. VBG, electrolytes q2-4h

**HYPEROSMOLAR HYPERGLYCEMIA**

- Hyperglycemia without ketoacidosis > osmotic diuresis > volume depletion > worsening hyperglycemia

- **TREATMENT:** Aggressive hydration with initially NS then ⅔ NS, average fluid loss up to 8-10 L, Insulin 10 U IV followed by 0.05 – 0.1 U/kg/h
## Thyroid Disorders

### Hyperthyroidism

#### Pathophysiology
- The thyroid gland produces thyroid hormones T3 and T4 in response to TSH (thyroid stimulating hormone) which is released from the pituitary in response to TRH (thyroid releasing hormone) from the hypothalamus.
- Thyroid hormones play a key role in metabolic process throughout the body.

#### Etiology
- **Grave’s disease** – autoimmune disorder – autoantibodies to TSH receptor, more common in females
- **Thyroiditis** – acute inflammatory disorder of the thyroid gland characterized by an initial hyperthyroidism followed by hypothyroidism then euthyroidism
- **Toxic adenomas** (single or multinodular goiter) – thyroid hormone production from a functioning adenoma
- **TSH-secreting pituitary tumor or pituitary resistance to thyroid hormone**
- **Medications** – amiodarone, iodine
- **Other** – struma ovarii, hCG secreting tumors, metastatic follicular thyroid cancer

#### Symptoms
- **General** – restless, anxious, tremor, weight loss, heat intolerance, increased appetite and thirst
- **Dermatology** – fine hair, moist/warm skin, pruritis
- **Cardiovascular** – palpitations
- **GI** – diarrhea
- **GU** – oligomenorrhea/amenorrhea, infertility

#### Signs
- **Vitals** – tachycardia, systolic hypertension, may have increased temperature
- **Ophthalmology** – stare and lid lag (seen in all types of hyperthyroidism)
- **Dermatology** – moist/warm skin, soft nails with onycholysis, palmar erythema
- **Neurology** – tremor, proximal muscle weakness and hyperreflexia
- **Cardiovascular** – atrial fibrillation
- **MSK** – osteoporosis
- **Grave’s Disease** – diffuse non-tender goitre + bruit, periorbital edema, lid retraction, proptosis, conjunctivitis, pretibial myxedema (non-pitting)

#### Investigations
- **General** – TSH, Free T3, T4
- **Radioactive Iodine Uptake and Scan (RAIU)** – contraindicated in pregnancy, not accurate if recently given IV contrast or amiodarone load
- **Thyrotropin receptor antibodies (TRAb)**

#### Management
- **Beta-blockers** – control tachycardia
- **Medication** – methimazole (1st line) or propylthiouracil (2nd line) (need to monitor LFTs, WBC)
- **Radioactive iodine**
  - May need to pretreat with antithyroid drugs to prevent worsening thyrotoxicosis
  - 75% become hypothyroid after treatment
- **Surgery (thyroidectomy)** – rare and usually option with obstructive goiter or ophthalmopathy
- **Ophthalmopathy**: can worsen after RAI, prophylaxis with prednisone in high risk patients, can be treated with radiation and surgical decompression
HYPOTHYROIDISM

ETIOLOGY

- Goiter present
  - Hashimoto’s thyroiditis – Autoimmune destruction of the thyroid. Characterized by the presence of anti-thyroid peroxidase and anti-thyroglobulin antibodies.
  - Iodine deficiency
  - Medications – lithium, amiodarone
- Goiter absent
  - Iatrogenic – thyroidectomy, surgical destruction, radioactive iodine therapy
- Central
  - Secondary hypothyroidism due to pituitary insufficiency (low TSH)
  - Secondary hypothyroidism due to hypothalamus insufficiency (low TRH)

SYMPTOMS

- General – fatigue, depression, cold intolerance, slowing mentally and physically, hoarseness
- Dermatology – cool and pale skin, dry skin and hair
- Cardiovascular – Worsening symptoms of CHF or angina
- Respiratory – Decreased exercise capacity, sleep apnea due to macroglossia
- GI – weight gain, constipation
- GU – menorrhagia, impotence
- Neurology – paresthesia, slow speech, muscle cramps, carpal tunnel syndrome

SIGNS

- Vitals – Diastolic hypertension, bradycardia. In the setting of severe hypothyroidism (myxedema crisis) – hypothermia, hypotension, hypoventilation, change in mental status.
- Dermatology – Puffiness of face, periorbital edema, eyebrows thinned (missing outer 1/3), macroglossia
- Neurology – delay in relaxation phase of deep tendon reflex (“hung reflex”)
- Cardiovascular – pericardial effusion, CHF

INVESTIGATIONS

- General – TSH, Free T3, T4
- Hashimoto’s disease suspected – Anti-TPO antibody
- May see hyponatremia, hypoglycemia, anemia, elevated LDL, decreased HDL, elevated CK

MANAGEMENT

- Levothyroxine 1.5 ug/kg/d, lower starting dose 0.5 ug/kg/d if elderly or hx CAD
- Titrate dose based on TSH q5-6wks

<table>
<thead>
<tr>
<th>INTERPRETING THYROID FUNCTION TESTS</th>
<th>TSH</th>
<th>Free T4</th>
<th>Free T3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subclinical hypothyroidism</td>
<td>Increased</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Primary hypothyroidism</td>
<td>Increased</td>
<td>Decreased</td>
<td>Decreased</td>
</tr>
<tr>
<td>Secondary hypothyroidism</td>
<td>Decreased</td>
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</tr>
<tr>
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<tr>
<td>Primary hyperthyroidism</td>
<td>Decreased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>T3 thyrotoxicosis</td>
<td>Decreased</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Secondary hyperthyroidism</td>
<td>Increased/Normal</td>
<td>Increased</td>
<td>Increased</td>
</tr>
</tbody>
</table>
**INTERPRETING RAIU**

<table>
<thead>
<tr>
<th>RESULT</th>
<th>DIAGNOSIS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse radioiodine uptake</td>
<td>• Homogenous – Grave’s disease</td>
</tr>
<tr>
<td></td>
<td>• Heterogenous – toxic multinodular goiter</td>
</tr>
<tr>
<td>Focal radioiodine uptake</td>
<td>• Functioning adenoma</td>
</tr>
<tr>
<td>No uptake</td>
<td>• Thyroiditis, exogenous thyroid hormone, recent iodine load, struma ovarii or antithyroid drugs</td>
</tr>
</tbody>
</table>

**ADDITIONAL INFORMATION – THYROID EMERGENCIES**

**THYROID STROM**

- **Definition** – Acute exacerbation of symptoms of thyrotoxicosis presenting in a life-threatening emergency, 20-50% mortality
- **Clinical features**
  - Vitals – Fever, tachycardia, hyperthermia, systolic hypertension, wide pulse pressures
  - General – Change in mental status (delirium, coma)
  - Cardiovascular – CHF, shock, tachyarrhythmia
  - GI – Vomiting, diarrhea, hepatic failure with jaundice and confusion
- **Treatment**
  - B-blocker, PTU or methimazole
  - Iodine 1h following PTU
  - Consider steroids to decrease T4 to T3 conversion

**MYXEDEMA CRISIS**

- **Definition** – severe hypothyroidism often precipitated by trauma, sepsis, cold exposure, MI which presents as a medical emergency
- **Clinical Features**
  - Vitals – Hypothermia, hypotension, hypoventilation
  - General – change in mental status including coma
  - Labs – Hyponatremia, hypoglycemia
- **Treatment**
  - Corticosteroids due to risk of associated adrenal insufficiency
  - Load IV T4 daily, may also give IV T3 q8h if unstable with bradycardia and suspected impaired peripheral conversion
  - Supportive measures as needed – mechanical ventilation, vasopressors, passive rewarming, IV dextrose, fluids
References

Approach to GI Bleed

GI Bleed

Upper GI Bleed (UGIB)
_Above ligament of Treitz_

- Peptic ulcer disease (20-67%)
- Erosive gastritis (4-31%)
- Erosive esophagitis (5-18%)
- Esophageal or gastric varices (4-20%)
- Mallory-Weiss tear (4-12%)
- Portal hypertensive gastropathy
- Vascular malformations (2-8%)
- Malignancy (2-8%)

Lower GI Bleed (LGIB)
_Below ligament of Treitz_

- Diverticular bleed (30%)
- Polyp/tumor (20%)
- Colitis (20%)
- Anorectal disorders (20%)
- Vascular (<10%)
- Meckel’s diverticulum
## GI BLEED

### DEFINITION
- Intraluminal blood loss anywhere from the oropharynx to the anus
- Severe GI bleed includes bleeding associated with shock, orthostatic hypotension, decreased hematocrit, or requiring transfusion ≥2 units packed red blood cells

### SYMPTOMS

#### GENERAL
- Symptoms of anemia – Fatigue, chest pain, palpitations, shortness of breath, presyncope, syncope
- UGIB – History of previous peptic ulcer; EtOH/ liver disease, NSAIDs or H. Pylori infection, anticoagulants, ASA, prior aortic surgery, change in bowel habits, weight loss, risk factors for cirrhosis
- LGIB – Past history of colon cancer, colon surgery, diverticulosis, hemorrhoids, radiation treatment
- Age
  - Young → Peptic ulcer, varices, esophagitis
  - Elderly → Diverticular disease, cancer

#### UGIB
- Hematemesis – blood in vomit
- Coffee ground emesis – blood exposed to gastric acid
- Melena – black and tarry stools from digested blood
- Hematochezia – bloody or maroon coloured stools + hemodynamic instability can be seen with brisk UGIB

#### LGIB
- Hematochezia
- Occult blood in stool
- Rarely melena but if present indicates GI bleed in right side of colon closer to ligament of Treitz

### SIGNS
- Vitals – tachycardia, hypotension or orthostatic hypotension, hypovolemic shock
- Anemia – pallor, weakness, cool, clammy skin
- Signs of chronic liver disease, lymphadenopathy, masses
- Rectal exam: masses, hemorrhoids, anal fissures, stool appearance

### INVESTIGATIONS
- Bloodwork: Hb, Hct, MCV, platelets, PT, PTT, BUN/Cr, LFTs
- Nasogastric tube: helps localize source of bleeding
  - Fresh blood or coffee grounds → Active or recent UGIB
  - No blood → does not exclude UGIB
- UGIB → EGD within 24 hr
  - Gastric lavage and erythromycin 250 mg IV 30 min prior to clear gastric contents
- LGIB → Colonoscopy (if severe bleed: within 12 hours)
  - If hematochezia + orthostasis, concern for brisk UBIG → exclude UGIB with EGD first
- Imaging: if too unstable for EGD
  - Tagged RBC scan: able to identify general location of bleed (bleeding rate >0.04 mL/min)
  - Arteriography: able to identify exact vessel bleeding (bleeding rate >0.5 mL/min)

### MANAGEMENT

#### INITIAL MANAGEMENT
- Assess hemodynamic stability – vital signs (including orthostatic changes), JVP
- Stabilize patient – 2 large bore IVs, IV fluids, monitor
- NPO status
- Transfusion – blood sample for type and cross; use O- in emergency
- Reverse coagulopathy – fresh frozen plasma and vitamin K (goal: platelets > 50,000)
- IV PPI – decrease risk of rebleed, stabilize clot
- Triage
  - If unstable vitals or poor end organ perfusion → ICU
  - If ongoing hematemesis, shock → emergent EGD
  - If sBP ≥110, HR <100, Hb ≥130 (males) or ≥120 (females), no melena, syncope, heart failure → consider outpatient management

### PEPTIC ULCER DISEASE
- PPI 80 mg IV bolus + 8 mg/h IV infusion
- Endoscopic therapy: epinephrine injection + bipolar cautery or hemoclip

### EROSIVE GASTROPATHY OR ESOPHAGITIS
- High-dose PPI

### ESOPHAGEAL OR GASTRIC VARICES
- Pharmacologic
  - Octreotide 50 μg IV loading dose + 50 μg/h IV infusion x 5 days
  - Antibiotic treatment → ceftriaxone improves mortality in patients with cirrhosis
- Nonpharmacologic → Endoscopic band ligation or sclerotherapy

### DIVERTICULAR DISEASE
- Usually spontaneous resolution in hours-days
- Endoscopic therapy: epinephrine injections ± electrocautery, hemoclip, banding
Approach to Chronic Diarrhea

Chronic Diarrhea

- Secretory
  - Bacterial toxins
  - Endocrine (Addison's, VIPoma, carcinoid, hyperthyroid)
  - GI neoplasm
  - Microscopic colitis
  - Bile acid

- Osmotic
  - Osmotic laxatives
  - Non-absorbable carbohydrates
  - Lactose intolerance

- Inflammatory
  - IBD (Chron's disease, ulcerative colitis)
  - Infectious (C. difficile, CMV)

- Malabsorption
  - Chronic pancreatitis
  - Celiac disease
  - Whipple's disease
  - Small intestinal bacterial overgrowth

- Functional
  - Irritable bowel syndrome
### CHRONIC DIARRHEA

#### DEFINITIONS
- **Acute diarrhea:** passage of frequent unformed stool for <14 days duration
- **Persistent diarrhea:** 14-30 days
- **Chronic diarrhea:** >4 weeks
- **Secretory diarrhea:** secretion of anions or K into lumen or inhibition of Na absorption
- **Osmotic diarrhea:** ingestion of poorly absorbed ions or sugars
- **Maldigestion/malabsorption:** defective intraluminal hydrolysis of nutrients or defective mucosal absorption of nutrients

#### SYMPTOMS
- Abnormally liquid/unformed stools of ↑ frequency
- **Timing** → relationship to meals, nocturnal diarrhea (suggests organic causes)
- **Associated symptoms** → abdominal pain, weight loss, prior surgery, chemotherapy or radiation
- **Precipitating agents** → PPI, colchicine, antibiotics, H2-receptor antagonists, SSRIs, ARBs, NSAIDs, chemotherapy, caffeine
- **Secretory** → watery, large volume, often nocturnal diarrhea, no abdominal pain, no fatty stool, no change in diarrhea w/ fasting
- **Osmotic** → watery, may be large or small volume, ↓ diarrhea w/ fasting or removal of offending agent
  - Lactose intolerance → bloating, flatulence, abdominal discomfort, diarrhea
- **Inflammatory** → abdominal pain, blood in stool
- **Maldigestion/ Malabsorption** → fatty diarrhea (steatorrhea), ↓ diarrhea w/ fasting
  - If celiac disease suspected assess for osteoporosis, dermatitis and herpetiformis
- **IBS** → watery diarrhea, chronic abdominal pain (relieved by defecation), mucus discharge, tenesmus, ↓ diarrhea w/ fasting
  - NOT IBS: large volume diarrhea, bloody or greasy stools, significant weight loss, anemia

#### SIGNS
- **Signs of hypovolemia** → tachycardia, ↓ BP, ↓ urine output, axillary dryness, skin turgor
- **General** → signs of systemic disease, surgical scars, rectal tone/DRE
- **Inflammatory** → fever, abdominal tenderness

#### INVESTIGATIONS

##### GENERAL
- Bloodwork: CBC, electrolytes, ESR, albumin, TSH, iron studies, celiac serology (IgA anti-tTg Ab)
- Stool analysis: *C. difficile* toxin, culture and sensitivity, ova and parasites, fecal fat, WBC, lactoferrin, calprotectin, fecal occult blood test
- Abdominal x-ray to rule out overflow diarrhea

##### ETIOLOGY
- Malabsorption → Θ Fecal fat
  - Celiac disease → IgA anti-tTg Ab, IgA levels, may require upper endoscopy for duodenal biopsy to confirm diagnosis
- Θ Fecal occult blood, WBC, fecal lactoferrin, calprotectin → Inflammatory
- Stool osmotic gap = 290 – [2 x (Na_{stool} + K_{stool})]
  - ≥100 → Osmotic
  - <100 → Secretory or Functional
- Colonoscopy if unknown cause
- Abdominal CT/MRI if systemic problem suspected
<table>
<thead>
<tr>
<th>Issue</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Oral hydration, loperamide, bismuth subsalicylate</td>
</tr>
<tr>
<td>Lactose intolerance</td>
<td>Lactose avoidance or lactase enzyme pill</td>
</tr>
<tr>
<td>Pancreatic insufficiency</td>
<td>Pancreatic enzyme replacement</td>
</tr>
<tr>
<td>Microscopic colitis</td>
<td>Antidiarrheals, cholestyramine, bismuth, budesonide</td>
</tr>
<tr>
<td>Bile acid-induced diarrhea</td>
<td>Cholestyramine (bile-acid binder)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>Avoidance of gluten</td>
</tr>
<tr>
<td>Whipple’s disease</td>
<td>Antibiotic therapy: Penicillin + Streptomycin or 3rd generation cephalosporin 10-14 days</td>
</tr>
<tr>
<td>Small intestinal bacterial overgrowth</td>
<td>Rifaximin or metronidazole for 7-10 days</td>
</tr>
<tr>
<td>IBS</td>
<td>Exercise, CBT, change in diet, probiotics</td>
</tr>
</tbody>
</table>
Approach to Splenomegaly

- Increased splenic demand
- Splenic infiltration
- Splenic congestion

Hematological
- Nutritional anemia
- Hemoglobinopathy
- Hemolysis
- Spherocytosis
- Sequestration
- Elliptocytosis

Infectious
- Viral: EBV, HIV, CMV
- Bacterial: Endocarditis, TB
- Parasitic: Malaria, histoplasmosis
- Fungal

Inflammatory
- SLE
- Sarcoidosis
- Felty syndrome
- Still’s disease

Non-malignant
- Benign metaplasia
- Cysts
- Amyloidosis
- Sarcoidosis
- Hamartoma
- Vascular abnormalities
- Lysosomal storage disease
- Glycogen storage disease

Malignant
- Leukemia: CML, CLL
- Lymphoproliferative disease
- Hodgkin lymphoma
- Myeloproliferative disorders
- Metastatic tumour

Mnemonic for causes of splenomegaly:
CHINA
- Cirrhosis/ Congestion (portal HTN)
- Hematological
- Infectious
- Neoplasm (malignant, non-malignant)
- Autoimmune
### SPLENOMEGALY

#### DEFINITIONS
- Splenomegaly: Abnormal enlargement of the spleen measured by size or weight
  - **Splenomegaly** → Length of 11-20 cm or weight 400-500 g
  - **Massive splenomegaly** → Length >20 cm or weight >1000 g

#### SYMPTOMS
- Constitutional symptoms (fever, weight loss), feeling of fullness in LUQ, early satiety
- Infectious symptoms (e.g., mononucleosis) → fever, chills and sweats, fatigue, sore throat, headache
- Past history → liver disease, hemolytic anemia

#### SIGNS
- **Inspection**
  - Bulging mass under left costal margin
  - Jaundice (scleral icterus, yellowing of skin), petechiae
  - Signs of chronic liver disease → Temporal wasting, parotid enlargement, asterixis, palmar erythema, thenar wasting, Dupuytren’s contracture, leukonychia, clubbing, caput medusae, ascites, peripheral edema
  - Signs of CHF → ↑ JVP, S3, crackles in lung fields, peripheral edema
- **Percussion**
  - Castell’s method → Percuss lowest left intercostal space at left anterior axillary line on full exhalation and inspiration
    - Castell’s sign: dullness on full inspiration may indicate splenomegaly
  - Traube’s space → Percuss in area bound by left 6th rib superiorly, left mid-axillary line laterally, and costal margin inferiorly
    - Test: dullness to percussion may indicate splenomegaly
- **Palpation**
  - Palpate RLQ → LUQ

#### INVESTIGATIONS
- **Bloodwork**: CBC, peripheral blood smear
  - As indicated: blood cultures, HIV, ANA, Rf, liver enzymes (AST, ALT, ALP, GGT), LFTs (platelets, INR, albumin, bilirubin), reticulocyte count, Monospot/EBV, haptoglobin, LDH
- **Imaging**: ultrasound abdomen/liver (to assess for cirrhosis and portal vein thrombosis), echocardiogram for cardiac function, CT (to rule out lymphoma and malignancy)
Approach to Jaundice

Jaundice

Unconjugated Hyperbilirubinemia

- Increased bilirubin production
  - Hemolysis (e.g., hemolytic anemia, sickle cell disease, thalassemia)
  - Extravasation of blood into tissues

- Extrahepatic cholestasis
  - Heart failure
  - Portosystemic shunt
  - Drugs (e.g., rifampin, probenecid, flavaspadic acid, bunamiodyl)

- Impaired bilirubin conjugation
  - Inherited:
    - Gilbert’s syndrome
    - Crigler-Najjar syndrome
  - Congenital:
    - Hyperthyroidism
    - Chronic hepatitis
    - Advanced cirrhosis

Conjugated Hyperbilirubinemia

- Impaired bilirubin uptake
  - Choledocholithiasis
  - Ascending cholangitis
  - Pancreatic cancer
  - Cholangiocarcinoma
  - Primary sclerosing cholangitis
  - Pancreatitis

- Intrahepatic cholestasis
  - Primary biliary cholangitis
  - Intrahepatic cholestasis of pregnancy
  - Corticosteroids

- Hepatocellular injury
  - Viral hepatitis
  - Alcoholic hepatitis
  - Medications
  - Nonalcoholic steatohepatitis
  - Hemochromatosis, Alpha-1-antitrypsin deficiency, Wilson’s, Celiac disease
  - Ischemic, congestive, Budd-Chiari
  - Infiltrative diseases
  - Autoimmune hepatitis
Approach to Altered Liver Enzymes

**Hepatocellular (elevated AST and ALT)**
- Viral hepatitis*: Hep A/B/C/D/E, CMV, EBC, HSV, VZV
- Autoimmune*
- Drugs/Toxins*: alcohol, acetaminophen
- Non-Alcoholic fatty liver
- Vascular*: ischemic, congestive, b dd-chiari
- Hereditary: hemochromatosis, alpha-1 antitrypsin deficiency, wilson’s*, celiac disease

*can cause AST/ALT >1000

**Cholestatic (elevated ALP and bilirubin)**
- Ductal dilation on ultrasound
- Biliary obstruction: cholecdocholithiasis, cholangiocarcinoma, pancreatic cancer, PSC

**Infiltrative (elevated ALP)**
- No ductal dilation on ultrasound/hepatocellular dysfunction
- Intrahepatic cholestasis: medications, TPN, sepsis, PBC
- Biliary epithelial damage: hepatitis, cirrhosis

- Malignancy: HCC, metastatic, lymphoma
- Granuloma: TB, sarcoidosis, histoplasmosis
- Abscess: Amoebic, bacterial
- Other: Medications, idiopathic

**Definitions**
- **Jaundice:** yellowish discoloration of the skin and mucous membranes caused by elevated serum bilirubin.
- **Unconjugated/ indirect bilirubin:** lipid-soluble product from metabolism of heme that travels through the bloodstream to the liver, where it is converted into conjugated bilirubin
- **Conjugated/ direct bilirubin:** water-soluble product of conjugation of unconjugated bilirubin by hepatocytes; component of bile; its by-products are responsible for the yellow colour of urine and brown colour of stool
- **Aminotransferases (AST, ALT):** intracellular enzymes released secondary to necrosis or inflammation, ALT more specific for liver than AST, also found in heart, skeletal muscle, kidney and brain
- **Alkaline phosphatase (ALP):** enzyme bound in hepatic canalicular membrane, increased levels seen with biliary obstruction or intrahepatic cholestasis, also found in bone, intestines, kidney, placenta
Cirrhosis

**CIRRHOSIS**

**DEFINITIONS**
- Irreversible scarring of the liver, common end stage of many chronic liver diseases
  - Stage 1 cirrhosis: compensated, asymptomatic, can last for 10-20 yrs
  - Stage 2 cirrhosis: decompensated

**PATHOPHYSIOLOGY**
- Cirrhosis impedes normal blood flow; resistance → blood backs up = portal HTN
  - Blood is redirected to vessels at anastomoses with the caval system: esophagus (→ varices), abdominal wall (→ caput medusae), stomach, rectum (→ hemorrhoids)

**ETIOLOGY**
- Viral hepatitis*: Hep A/B/C/D/E, CMV, EBC, HSV, VZV
- Alcohol*
- Medications: amiodarone, methotrexate
- Autoimmune hepatitis
- Non-Alcoholic fatty liver disease*
- Vascular: congestive, constrictive pericarditis, budd-chiari
- Hereditary: hemochromatosis, alpha-1 antitrypsin deficiency, wilson’s, celiac disease
- Cholestatic: PBC, PSC, biliary obstruction
  *most common causes of cirrhosis

**COMPLICATIONS**
- Gastroesophageal varices: increased blood flow through esophageal veins due to portal HTN → venous dilation → gastrointestinal bleed
- Ascites: portal hypertension → systemic vasodilatation → decreased effective circulating volume → renal sodium retention → volume overload
- Spontaneous bacterial peritonitis: spontaneous bacterial translocation from gut to ascitic fluid
- Hepatorenal syndrome: splanchnic vasodilatation leading to activation of RAAS and renal vasoconstriction leading to decreased in renal blood flow with a structurally normal kidney
- Encephalopathy: failure of liver to detoxify ammonia and other substances that cause cerebral edema
- Infection
- Coagulopathy
- Hepatocellular carcinoma (HCC)

**SYMPTOMS**
- Symptoms of cirrhosis: anorexia, fatigue, pruritis, N/V, dark-coloured urine
- Symptoms of complications
  - Variceal bleeds: melena
  - Ascites: increased abdo girth, increased weight, dyspnea, early satiety
  - Hepatorenal syndrome: decreased urine output
  - Infection/sepsis: fever, abdominal pain
  - Coagulopathy: easy bruising
  - Encephalopathy: sleep wake reversal, poor concentration, personality changes
  - HCC: weight loss

**SIGNS – stigmata of chronic liver disease**
- Signs of cirrhosis
  - Head: temporalis muscle wasting, parotid gland enlargement, jaundice, scleral icterus
  - Hand: asterixis, palmar erythema/edema, thenar muscle wasting, Dupuytren’s contracture
Nails: clubbing, half and half nails, leukonychia
  • Chest: spider nevi, painful gynecomastia
  • Abdomen: hepatosplenomegaly (splenomegaly develops 1st), caput medusae
  • Legs: edema
  • Anogenital: hemorrhoids, testicular atrophy
• Signs of complications
  • Variceal bleeds: black tarry stool on DRE, hypotension, shock
  • Ascites: bulging flanks, + shifting dullness and + fluid wave tests, ankle edema
  • Encephalopathy: confusion

INVESTIGATIONS
• Bloodwork
  • CBC: anemia of chronic disease, neutropenia and thrombocytopenia from increased splenic sequestration
  • Liver enzymes: high ALT and AST suggest injury to hepatocytes, high ALP and GGT suggest injury to bile duct cells
  • Liver function: Elevated INR, decreased albumin, elevated bilirubin
  • Kidney function: elevated Cr (if AKI/hepatorenal syndrome)
  • Determine etiology: hepatitis serologies (HBsAg, Anti-HBs, anti-HCV), autoimmune hepatitis studies (IgG, ANA, Anti-smooth muscle Ab), Fe and Cu studies, alpha1 antitripsin, AMA
• Imaging
  • Abdo US with doppler: cirrhosis FU every 6 mths to look for HCC
  • FibroScan: predict degree of fibrosis
• Liver biopsy: definitive diagnosis of cirrhosis and diagnose etiology
• Diagnostic paracentesis (in decompensated cirrhosis, need to rule out SBP!!)
  • SAAG > 11 g/L = Portal HTN related
    • Cirrhosis (AFTP <2.5g/L), acute hepatitis, HCC
    • Hepatic congestion: right heart failure (AFTP >2.5g/L), Budd-Chiari
    • Portal or splenic vein thrombosis
  • SAAG <11 g/L = Not associated with portal HTN
    • Malignancy: peritoneal carcinomatosis
    • Infection: TB
    • Inflammatory: pancreatitis
    • Hypoalbuminemia: nephrotic syndrome, protein-losing enteropathy

MANAGEMENT
• Decrease liver damage: abstain from alcohol, avoid hepatotoxic drugs, Hep A and B vaccines if non-immune
• Treat complications:
  • Variceal bleeds: for primary prevention all patients should be screened with EGD and for med-large varices treat with nonselective beta blockers (nadolol, propranolol, carvedilol) or endoscopic variceal ligation; In acute bleed treat with fluid resuscitation, blood transfusion, IV octreotide, urgent EGD with band ligation, start non-selective beta-blockers, once stable
    • if recurrent bleeding ➔ TIPS
  • Ascites: salt restriction, diuretics, large volume paracentesis + IV albumin if refractory
    • if still uncontrolled ➔ TIPS
  • Hepatorenal syndrome: volume resuscitation + albumin, hold diuretics and other nephrotoxic meds, octreotide and midodrine
  • SBP: IV Ceftriaxone x 5 days, IV albumin on day 1 and 3, indefinite prophylaxis if history of SBP
  • Coagulopathy: fresh frozen plasma, cryoprecipitant if bleeding or evidence of DIC
  • Encephalopathy: rule out precipitants (bleeding, infection, electrolyte abdnormalities, PVT, meds), lactulose (laxative) titrate to 2-4 bowel movements per day, rifaximin (antibiotic)
• HCC: radiofrequency ablation for HCC < 3cm, resection if 1 lesion <2cm and Child-Pugh A, TACE (noncurative) for large cancers not amenable to RFA, liver transplant if ≤3 lesions ≤3cm or 1 lesion ≤5cm

• Liver transplant: Evaluation when MELD >15. Refer earlier if recurrent encephalopathy, refractory ascites, recurrent variceal bleeding, hepatopulmonary syndrome, acute liver failure
## Viral Hepatitis

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Hepatitis A (ssRNA)</th>
<th>Hepatitis B (dsDNA)</th>
<th>Hepatitis C (ssRNA)</th>
<th>Hepatitis D (RNA)</th>
<th>Hepatitis E (ssRNA)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Consuming contaminated food, water, shellfish</td>
<td>- IV drug use</td>
<td>- IV drug use</td>
<td>- IV drug use</td>
<td>- HepB infection</td>
<td>- Travel to central Asia, south-east Asia, Mexico</td>
</tr>
<tr>
<td>- High risk sexual activity</td>
<td>- High risk sexual activity</td>
<td>- High risk sexual activity</td>
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</tr>
</thead>
<tbody>
<tr>
<td>- Sexual activity</td>
<td>- Perinatally</td>
<td>- Sexual activity</td>
<td>- Requires HepB coinfection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Incubation Period</th>
<th>2wk – 6wk</th>
<th>6wk – 6mo</th>
<th>1mo – 5mo</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Presentation</th>
<th>Decreased appetite, fatigue, nausea, malaise, fever, jaundice, RUQ pain</th>
<th>-70% sub-clinical</th>
<th>-80% sub-clinical</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- 30% jaundice</td>
<td>- 10-20% mild and vague fatigue, malaise, nausea, jaundice</td>
<td>- Extrahepatic symptoms (arthritis, membranous nephropathy, membranoproliferative glomerulonephritis, PAN)</td>
</tr>
<tr>
<td></td>
<td>- &lt;1% fulminant liver failure</td>
<td>- Extrahepatic symptoms (mixed cryoglobulinemia, lichen planus, thyroiditis, etc.)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disease Course</th>
<th>Acute infection rarely fulminant</th>
<th>-5% becomes chronic</th>
<th>-80% becomes chronic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Never chronic infection</td>
<td>-40% develop cirrhosis</td>
<td>-20% develop cirrhosis</td>
</tr>
<tr>
<td></td>
<td>Causes more aggressive disease than HBV alone</td>
<td></td>
<td>- Can result in acute liver failure with acceleration of progression to cirrhosis</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Acute: +/ - anti-HAV IgM</th>
<th>Chronic: +/ - anti-HAV IgG</th>
<th>Acute: +/ - anti-HCV IgM</th>
<th>Chronic: +/ - anti-HCV IgG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>See Table below</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Hepatitis B – Viral Markers

<table>
<thead>
<tr>
<th>Serologic Markers</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBsAg</td>
<td>anti-HBs</td>
</tr>
<tr>
<td>⊖</td>
<td>⊖</td>
</tr>
<tr>
<td>⊗</td>
<td>⊗</td>
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</tbody>
</table>

- Hepatitis B surface antigen (HBsAg), Hepatitis B surface antibody (anti-HBs), IgM antibody to Hepatitis B core antigen (IgM anti-HBc), IgG antibody to Hepatitis B core antigen (IgG anti-HBc), Hepatitis B envelope antigen (HBeAg), Hepatitis B envelope antibody (anti-HBe), Hepatitis B DNA (HBV DNA)
### Pancreatitis

#### ACUTE PANCREATITIS

**DEFINITION**
- Inflammation of the pancreas due to impaired secretion and premature activation of enzymes causing autodigestion of the pancreas

**DIAGNOSTIC CRITERIA**
- Diagnosis requires 2 out of 3 of the following
  1. Characteristic abdominal pain
  2. Lipase or amylase > 3X upper limited of normal
  3. Positive imaging

**ETIOLOGY**
- *I GET SMASHED* – Idiopathic, gallstones (40% of the cases), ethanol (30% of the cases), trauma, steroids, surgery, sphincter of Oddie dysfunction, microbiological (mumps, TB, rubella, campylobacter, varicella), autoimmune, scorpion bite, hyperlipidemia, hypercalcemia, hypothermia, ERCP, drugs (5-ASA, 6-MP/ZA, ACEI, diuretics, antibiotics, statins)

**SYMPTOMS**
- Epigastric abdominal pain which can be bandlike and radiate to back
- Nausea and vomiting

**SIGNS**
- Vitals – fever, tachycardia, hypotension, low O2 sats (due to ARDS)
- General inspection – Distressed, diaphoretic, hypovolemic, jaundice if biliary obstruction
- Abdominal exam
  - Signs of peritonitis – guarding and rebound tenderness
  - Signs of retroperitoneal hemorrhage – Cullen’s sign, Grey-Turner’s sign

**INVESTIGATIONS**
- Bloodwork
  - CBC – leukocytosis
  - Pancreatic enzymes – elevated amylase, *elevated lipase* > 3X upper limit of normal (more sensitive and specific than amylase)
  - Liver enzymes – elevated ALP/GGT, bilirubin if secondary to gallbladder disease
  - Renal function – elevated creatinine and BUN secondary to AKI from hypovolemia
- Imaging
  - Abdominal U/S – not useful in evaluating pancreas but should be ordered to rule out biliary causes
  - Abdominal CT with contrast – consider if diagnosis is unclear or if persistent pain and clinical deterioration in 48-72hrs. Can be used to rule out local complications.
  - ERCP – evaluate and treat cholangitis or choledocholithiasis
  - MRCP – assess for necrosis or biliary disease

**MANAGEMENT**

**PROGNOSIS**
- Ranson’s criteria – predicts severity at admission and after 48hrs
  - At admission – Age >55yr, WBC >16 x 10^6, glucose > 11 mmol/L, LDH ≥350 IU/L, AST >250 IU/L
  - During initial 48hrs – HCT >10%, BUN rise> 1.8mmol/L, arterial PO₂ <60mmHg, base deficit >4mmol/L, calcium <2mmol/L, fluid sequestration >6L
  - ≥2 = difficult course and ≥3 = high mortality

**TREATMENT**
- Fluid resuscitation – early aggressive IV fluid with Ringer’s Lactate
### Complications

- **Systemic complications** – Acute respiratory distress syndrome, AKI, GI bleed, DIC
- **Metabolic complications** – hypocalcaemia, hyperglycemia, hypertriglyceridemia
- **Fluid collections** – acute fluid collection or pseudocyst (no tx if asymptomatic but drainage if symptomatic)
- **Necrosis**
  - Sterile necrosis - no treatment if asymptomatic
  - Infected necrosis – antibiotic treatment and percutaneous drainage
  - Pancreatic abscess – collection of pus with no pancreatic tissue requires antibiotics and percutaneous drainage

### Chronic Pancreatitis

#### Definition
- Chronic inflammation of pancreas with irreversible damage that is often due to recurrent acute attacks leading to inflammation → fibrosis → pancreatic insufficiency
- Pancreatic insufficiency leads to loss in exocrine and endocrine function which can lead to decrease insulin production/excretion and decrease production of pancreatic enzymes
- Chronic inflammation leads to increased risk of pancreatic cancer

#### Etiology
- 60-80% due to alcohol consumption
- Other causes include smoking, idiopathic, genetic, autoimmune, recurrent acute pancreatitis and gallbladder disease, cystic fibrosis

#### Symptoms
- Chronic epigastric pain radiating to the back that can be aggravated by food ingestion – may have no pain
- Exocrine insufficiency → fat malabsorption → steatorrhea

#### Signs
- Exocrine insufficiency → Weight loss
- Endocrine insufficiency → Diabetes

#### Investigations
- **Bloodwork**
  - Amylase and lipase may be elevated early in the course but usually normal
  - HbA1c or fasting blood glucose → elevated in diabetes
  - Genetic testing in younger individuals → IgG4, ANA, CFTR, etc.
  - Liver enzymes: elevated ALP, elevated bilirubin less common
- **Stool analysis** – decreased stool elastase and positive fecal fat
- **Imaging** – abdominal US or CT with contrast – calcification, dilated pancreatic ducts, pseudocyst

#### Management
- **Lifestyle modification** – total abstinence from alcohol and smoking cessation, eat smaller, more frequent meals with lower fat content
- **Pain management** – analgesics, ESWL if stone, celiac nerve plexus block
- **Pancreatic enzyme supplementation**
- **Recognize and address complications** – pseudocyst, pseudoaneurysms, pancreatic ascites, pleural effusion, pancreatic cancer

#### Nutrition
- **Mild pancreatitis** – NPO until pain free without ileus then advance low-fat diet as tolerated
- **Severe** – NPO then enteral nutrition after 48-72h

#### Analgesia
# Inflammatory Bowel Disease

## Definitions

- **Crohn’s disease (CD):** *transmural* inflammation occurring anywhere in GI tract (mouth to perianal region); *skip lesions*
  - Classification by location: small bowel (47%), ileocolonic (21%), colonic (28%)
  - Epidemiology: bimodal presenting at 15-30yo and 50-70yo
  - Histology: transmural inflammation, noncaseating granulomas, fibrosis, ulcers, fissures
- **Ulcerative colitis (UC):** inflammation of the colonic *mucosa*; starting at rectum and can extend to cecum; *contiguous*
  - Classification by location: proctitis (25-55%), left-sided colitis (50-70%), pancolitis (20%)
  - Histology: superficial chronic inflammation, crypt abscesses
- **Pseudomembranous colitis (PMC):** inflammation of the colon, usually associated with *C. difficile* infection, characterized by elevated yellow-white plaques that coalesce to form pseudomembranes on the mucosa

## Symptoms

- Symptoms of CD – *Abdominal cramps*, loose/frequent stools, fever, malaise, weight loss, mucus-containing, *non-grossly bloody diarrhea*; nausea/vomiting, bloating if obstruction
- UC – Rectal bleeding, *grossly bloody diarrhea*, lower abdominal cramps (especially with defecation), urgency, tenesmus, incontinence; anorexia, weight loss, fatigue if severe
- PMC – Abdominal pain, diarrhea, fever, leukocytosis

## Signs

- Abdominal tenderness
- Signs of complications – *see table below*

## Investigations

- Bloodwork: CBC, LFTs, iron, vitamin B12, folate, vitamin D, ESR, CRP
- Fecal calprotectin and lactoferrin, suggestive of intestinal inflammation
- Bacterial cultures, ova and parasites, *C. difficile* toxin to exclude other causes of inflammatory diarrhea
- CD → Ileocolonoscopy + biopsy; CT/MR enterography to visualize small bowel
- UC → Colonoscopy; Barium enema (*lead pipe sign*)
- PMC → *C. difficile* stool testing; endoscopy for diagnosis

## Management

### Crohn’s Disease

- **Mild** → Sulfasalazine (5-ASA) 4-6 g/d to induce *remission*
- **Mild-moderate** → Budesonide PO
- **Moderate-severe** → Prednisone 40-60 mg PO w/ taper over wks to induce *remission*
  - → Azathioprine/ 6-mercaptopurine 0.5-1 mg/kg and increase over wks for *maintenance*
  - → Methotrexate 15-25 mg IM/SC or PO qwk for *maintenance*
- **Severe/ refractory disease** → Anti-TNF (e.g., infliximab)
  - → Colonic resection if refractory

### Ulcerative Colitis

- **Mild** → 5-ASA (mesalamine) to induce *remission* and for *maintenance*
- **Mild-moderate** → MMX-budesonide PO for flares
- **Moderate-severe** → Prednisone 40-60 mg PO w/ taper over wks to induce *remission*
  - → Azathioprine/ 6-mercaptopurine 0.5-1 mg/kg and increase over wks for *maintenance*
- **Severe/refractory disease** → Hydrocortisone 100 mg q8h or Methylprednisolone 16-20 mg q8h to induce *remission* w/ plan to taper and switch to non-steroid maintenance
  - If refractory to steroids, consider:
    - Cyclosporine 2-4 mg/kg IV x7 days
    - Anti-TNF (e.g., infliximab) if refractory to steroids
    - Colectomy (ileal pouch-anal anastomosis (IPAA))

### EXTRACOLONIC MANIFESTATIONS OF IBD

<table>
<thead>
<tr>
<th>Condition</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythema Nodosum</td>
<td>Px → Raised, tender, red or violet subcutaneous nodules 1-5 cm in diameter with symmetric distribution; extensor surfaces of extremities (e.g., anterior tibial area)</td>
</tr>
<tr>
<td>Pyoderma Gangrenosum</td>
<td>Hx → Previous trauma</td>
</tr>
<tr>
<td></td>
<td>Px → Single or multiple erythematous papules/pustules; subsequent necrosis and ulcerations that are painful, deep, with violaceous undermined border and necrotic purulent centre; commonly affects shins</td>
</tr>
<tr>
<td>Peripheral Arthritis</td>
<td>Hx → Asymmetrical large-joint oligoarthritis, most often involving lower limbs; migrates from joint to joint</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>Hx → Inflammatory back pain; improves with exercise/hot water/NSAIDs; no improvement with rest; pain at night; morning stiffness</td>
</tr>
<tr>
<td></td>
<td>Px → Progressive limitation of spine motion</td>
</tr>
<tr>
<td>Uveitis</td>
<td>Hx → Bilateral, insidious onset, long-lasing, eye pain, blurred vision, photophobia, headaches</td>
</tr>
<tr>
<td></td>
<td>Px → Ciliary flush (redness most intense at limbus, radiating outward a short distance)</td>
</tr>
<tr>
<td>Episcleritis</td>
<td>Hx → Unilateral, foreign body sensation (feels hot/prickly, minimal pain), minimal vision changes</td>
</tr>
<tr>
<td></td>
<td>Px → Hyperaemic sclera and conjunctiva; topical 10% phenylephrine will blanch vessels</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>Hx → Asymptomatic (80%); biliary colic (pain in RUQ or epigastrium), vomiting</td>
</tr>
<tr>
<td></td>
<td>Px → Murphy’s sign, tenderness in RUQ or epigastrium, fever, jaundice</td>
</tr>
<tr>
<td>Primary sclerosing cholangitis</td>
<td>Hx → May be asymptomatic; insidious abdominal pain, pruritis, chills, fatigue</td>
</tr>
<tr>
<td></td>
<td>Px → Acholic stools, Dark urine, fever, jaundice</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>Hx → Flank pain, nausea, vomiting, frequency, urgency</td>
</tr>
<tr>
<td></td>
<td>Px → Hematuria, diaphoresis, tachycardia, tachypnea</td>
</tr>
</tbody>
</table>
References
Hematology
Approach to Anemia

Anemia

- Microcytic (MCV <80)
  - TAILS
    - Thalassemia
    - Anemia of chronic disease
    - Iron deficiency
    - Lead poisoning
    - Sideroblastic

- Macrocytic (MCV >100)
  - BALDRAT
    - B12/folate deficiency
    - Alcohol
    - Liver disease
    - Drugs (MTX, sulfa, chemo)
    - Reticulocytosis
    - Aplastic anemia
    - Hypothyroidism

- Normocytic (MCV 80-100)

  INCREASED DESTRUCTION
  - Autoimmune hemolytic anemia
  - RBC membrane – spherocytosis
  - RBC enzymes – G6PD, pyruvate kinase deficiency
  - Sickle cell anemia
  - Microangiopathic – DIC, TTP, prosthetic valve, HTN crisis

  DECREASED PRODUCTION
  - Bone marrow disorder
  - Decreased EPO from CKD
  - Anemia of chronic disease

  SEQUESTRATION
  - Splenomegaly

  ACUTE BLOOD LOSS

62
ANEMIA

DEFINITIONS
- HCT <41% OR HGB <135g/L in males
- HCT <36% OR HGB <120g/L in females

SYMPTOMS
- General
  - Low RBC mass → low O₂ delivery to tissue → fatigue, exertional dyspnea, chest pain
- Symptoms suggesting underlying etiology
  - Bleeding (menstrual history is women)
  - Systemic illness, constitutional symptoms
  - Drug use
  - Exposure (ex. Lead)
  - Alcohol use, risk factors for liver disease
  - Yellowing of the skin, dark urine (symptoms in hemolysis)
  - Diet – vegetarian, vegan (B12 or folate deficiency)
  - Family history of anemia (ex. Thalassemia or sickle cell)

SIGNS
- General
  - Vitals: tachycardia, orthostatic hypotension
  - Pallor (mucous membranes, palmar creases)
- Signs suggesting underlying etiology
  - Jaundice → hemolysis, liver disease
  - Splenomegaly → thalassemia, neoplasm, chronic hemolysis
  - Petechiae/purpura → bleeding disorder
  - Glossitis → iron, folate, B12 deficiency
  - Koilonychia → iron deficiency
  - Neurological abnormalities → B12 deficiency

INVESTIGATIONS

GENERAL
- CBC w/ differential, MCV and reticulocyte count
- Peripheral smear

MICROCYTIC ANEMIA
- Serum iron, serum ferritin, TIBC, transferrin saturation
- FOBT and/or endoscopy unexplained iron deficiency anemia, need to assess for GI bleed
- Hemoglobin electrophoresis if suspect thalassemia

<table>
<thead>
<tr>
<th></th>
<th>Ferritin</th>
<th>Iron</th>
<th>TIBC</th>
<th>% Transferrin saturation</th>
<th>Blood smear</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalassemia</td>
<td>Normal</td>
<td>Increased</td>
<td>Decreased</td>
<td>Increased</td>
<td>Target cells</td>
</tr>
<tr>
<td>Anemia of Chronic Disease</td>
<td>Normal/Increased</td>
<td>Decreased</td>
<td>Normal/Decreased</td>
<td>Normal/Decreased</td>
<td>Microcytic cells</td>
</tr>
<tr>
<td>Iron Deficiency</td>
<td>Decreased</td>
<td>Decreased</td>
<td>Increased</td>
<td>Decreased</td>
<td>Microcytic and hypochromic</td>
</tr>
<tr>
<td>Sideroblastic</td>
<td>Normal/Increased</td>
<td>Normal/Decreased</td>
<td>Normal/Decreased</td>
<td>Normal/Decreased</td>
<td>Stippled cells Ringed sideroblasts</td>
</tr>
</tbody>
</table>
NORMOCYTIC ANEMIA
- Decreased production
  - Creatinine
  - TSH
  - AST, ALT, ALP, Bilirubin, INR, PTT
- Increased destruction
  - Low haptoglobin, high bilirubin, high LDH – hemolysis
  - Direct Coombs test (DAT)
    - DAT positive = immune hemolytic anemia
      - Autoimmune, drug-induced, alloimmune
    - DAT negative = non-immune hemolytic anemia
      - TTP/HUS, DIC, hemoglobinopathies, hereditary spherocytosis
- EGD/colonoscopy may be required if evidence of acute blood loss from GI source
- Ultrasound if splenomegaly suspected
- Further investigations may be required for malignancy or diseases of chronic inflammation
- Bone marrow biopsy and aspirate
- Serum protein electrophoresis

MACROCYTIC ANEMIA
- Vitamin B12
- Folate
- TSH
- AST, ALT, ALP, bilirubin – liver disease
- INR, PTT

MANAGEMENT
GENERAL
- Blood transfusion for severe (HgB<70g/L) and symptomatic anemia – see transfusion section for more details
- Identify etiology and treat the cause

MICROCYTIC ANEMIA
- Iron deficiency → Iron supplement – iron sulfate, iron gluconate, IV iron.
- Thalassemia → folate supplement, transfusions + Fe chelator, splenectomy considered if over 50% increase in transfusion requirements

NORMOCYTIC ANEMIA
- CKD → Erythropoietin
- Warm autoimmune hemolytic anemia → corticosteroids, splenectomy, IVIG, cytotoxic agents, rituximab
- Cold autoimmune hemolytic anemia → Avoid cold, steroids ineffective, rituximab
- TTP → urgent plasma exchange
- DIC → treat underlying disease/infection

MACROCYTIC ANEMIA
- Folate deficiency → folate
- B12 deficiency → vitamin B12
- Hypothyroidism → levothyroxine
Approach to Abnormal Hemostasis

- Increased destruction
- Platelet Disorder
- Coagulopathy
- Decreased platelet function
- Thrombocytopenia
- Decreased production
- Increased destruction
- Splenic sequestration/dilutional

- Congenital
- Acquired
- - Hemophilia
- - vWD
- - Medications
- - Liver disease
- - Vit K deficiency
- - DIC
- - Medications
- - Uremia
- - Aplastic anemia
- - Alcohol
- - Cirrhosis
- - Leukemia
- - MDS
- - Immune mediated: primary (ITP), secondary (HIV, HCV, SLE, PS, CLL, heparin)
- - Non-immune mediated: MAHA (DIC, HUS, TTP), vasculitis, HELLP, cardiopulmonary bypass
- - vWD
- - Aplastic anemia
- - Alcohol
- - Cirrhosis
- - Leukemia
- - MDS
- - vWD
- - Medications
- - Uremia
## ABNORMAL HEMOSTASIS

### BACKGROUND

“The clotting process is a dynamic, highly interwoven array of multiple processes. Different phases include: endothelial injury and formation of platelet plug > propagation of the clotting process by the coagulation cascade > termination of clotting by antithrombotic control mechanisms > removal of the clot by fibrinolysis.”

### DEFINITIONS

- **Immune mediated thrombocytopenia (ITP)** – immune mediated destruction of platelets due to antiplatelet autoantibodies
- **Thrombotic thrombocytopenic purpura (TTP)** – vascular occlusive disorder characterized by thrombocytopenia, microangiopathic hemolytic anemia, change in mental status, fever renal failure
- **Disseminated intravascular coagulation (DIC)** – activation of coagulation from trauma, shock, infection, malignancy, obstetrics, leading to thrombosis and acute consumption of coagulation factors and platelets which leads to bleeding
- **Von Willebrand’s disease (vWD)** – quantitative (type 1) or qualitative (type 2) deficiency in vWF which acts as platelet “glue” and carrier for factor VII

### SYMPTOMS

- **General** – Medications (ex. Blood thinners, anti-platelets), alcohol use, recent infections, history of malignancy, constitutional symptoms, liver disease, autoimmune disease, family history of bleeding disorders
- **Coagulopathy**
  - Deep and soft tissue bleeding (ex. Bleeding of joints, muscles, etc.)
  - Delayed and severe bleeding after surgery
- **Platelet disorders**
  - Skin and mucus membranes bleeding (ex. Gum bleeding, nose bleeds)
  - Prolonged bleeding after mild cuts
  - Immediate and mild bleeding after surgery

### SIGNS

- **General** – Rule out active bleeding, splenomegaly, lymph nodes, signs of liver disease and autoimmune disease
- **Coagulopathy** – Hemarthroses, hematomas
- **Platelet disorders** – Petechiae, ecchymoses

### INVESTIGATIONS

#### PLATELET DISORDERS

- **Thrombocytopenia**
  - CBC w/ differential
  - Peripheral smear
    - Increased destruction → look for large platelets, schistocytes (DIC, TTP, HUS)
    - Decreased production → look for blasts, hypersegmented PMNs, leukoerythroblastic (aplastic anemia, MDS, leukemia)
  - Additional laboratory investigations as indicated: reticulocyte count, LDH, haptoglobin, bilirubin, INR, PTT, fibrinogen, D-Dimer, Coombs, ANA, APLA, flow cytometry, viral titres
  - Bone marrow biopsy – for unexplained thrombocytopenia

#### Disorders of platelet function

- To test platelet function - platelet aggregation test
- To test for Von Willebrand’s disease - vWF:Ag, vWF activity, factor VIII, vWF multimer analysis

#### COAGULOPATHIES

- PT, INR, mixing study, coagulation factor levels
- If DIC suspected – fibrinogen, FDPs, d-dimer
<table>
<thead>
<tr>
<th>Factor Deficiency</th>
<th>PT</th>
<th>PTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemophilia A</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>Hemophilia B</td>
<td>Normal</td>
<td>Increased</td>
</tr>
<tr>
<td>DIC</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Increased</td>
<td>Normal</td>
</tr>
<tr>
<td>Vitamin K deficiency</td>
<td>Increased</td>
<td>Normal</td>
</tr>
</tbody>
</table>

**MANAGEMENT**

**PLATELET DISORDERS**
- ITP → steroids and IVlg. Splenectomy, rituximab, romiplostim if refractory.
- TTP/HUS → urgent plasma exchange +/- glucocorticoids
- vWD → desmopressin (dDAVP), vWF replacement (cryoprecipitate)
- Uremia → dDAVP, cryoprecipitate, correct anemia

**COAGULOPATHY**
- Hemophilia A → purified/recombinant factor VIII, dDAVP if mild, cryoprecipitate, amino-caproic acid
- Hemophilia B → purified/recombinant factor IX
- DIC → support with fresh frozen plasma, cryoprecipitate, platlets
## Venothromboembolic Disease

### VTE

#### DEFINITIONS
- Formation of an thrombus or embolism within the venous system
  - Deep vein thrombosis → thrombosis formation in proximal veins (ex. iliac, femoral or popliteal) or distal veins (ex. Calf veins below the knee)
  - Pulmonary embolism → thrombosis originating in the venous system and embolizing to the pulmonary arterial circulation

#### DIFFERENTIAL DIAGNOSIS
- Vascular: venous insufficiency, superficial thrombophlebitis
- Lymphatic: lymphedema (chronic)
- Drugs: calcium channel blockers
- Other: Cellulitis, necrotizing fasciitis, knee injury, calf muscle tear, Baker cyst rupture

#### PATHOPHYSIOLOGY
- Virchow’s Triad
  - Venous stasis – bed rest, inactivity, CHF, CVA, air travel >6h
  - Endothelial injury – trauma, surgery, prior DVT, central catheter, inflammation
  - Hypercoagulable state – pregnancy, OCP, hormone replacement, Factor V Leiden deficiency

#### SYMPTOMS
- DVT – calf pain, unilateral leg swelling and redness
- PE – SOB, pleuritic chest pain, cough, hemoptysis, syncope/presyncope, symptoms of DVT

#### SIGNS

##### DVT
- General → distension of collateral superficial veins, unilateral calf swelling, erythema and warmth
- Palpation → pitting edema, pain on palpation of the calf, palpable cord
- Homan’s sign → calf pain with dorsiflexion of the foot
- Phlegmasia cerulea dolens → massive proximal DVT with cyanosis, edema, pain, compartment syndrome
- Phlegmasia alba dolens → associated arterial spasm, cold and pale limb, weak pulse

<table>
<thead>
<tr>
<th>DVT – Well's Score</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active cancer (treatment ongoing, administered within previous 6 months or palliative)</td>
<td>+1</td>
</tr>
<tr>
<td>Paralysis, paresis, or recent plaster immobilization of the lower extremities</td>
<td>+1</td>
</tr>
<tr>
<td>Recently bedridden &gt;3 days or major surgery within previous 12 weeks requiring general or regional anesthesia</td>
<td>+1</td>
</tr>
<tr>
<td>Localized tenderness along the distribution of the deep venous system</td>
<td>+1</td>
</tr>
<tr>
<td>Swelling of entire leg</td>
<td>+1</td>
</tr>
<tr>
<td>Calf swelling &gt;3 cm larger than asymptomatic side (measured 10 cm below tibial tuberosity)</td>
<td>+1</td>
</tr>
<tr>
<td>Pitting edema confined to the symptomatic leg</td>
<td>+1</td>
</tr>
<tr>
<td>Collateral superficial veins (nonvaricose)</td>
<td>+1</td>
</tr>
<tr>
<td>Previously documented DVT</td>
<td>+1</td>
</tr>
<tr>
<td>Alternative diagnosis at least as likely as DVT</td>
<td>-2</td>
</tr>
</tbody>
</table>

* A score of 2 or higher indicates that the probability of DVT is “likely”; a score of less than 2 indicates that the probability is “unlikely”
## Vitals
- Tachypnea, tachycardia, hypoxemia, fever, hypotension

## CV and RESP exam
- Cyanosis, pleural friction rub, loud P2

## Massive PE
- Right sided heart strain → syncope, hypotension, PEA, elevated JVP

### PE – Wells’ Score

<table>
<thead>
<tr>
<th>Score</th>
<th>PE – Wells’ Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous DVT/PE</td>
<td>+1.5</td>
</tr>
<tr>
<td>HR &gt; 100</td>
<td>+1.5</td>
</tr>
<tr>
<td>Recent immobilization or surgery</td>
<td>+1.5</td>
</tr>
<tr>
<td>Clinical signs of DVT</td>
<td>+3</td>
</tr>
<tr>
<td>Alternate diagnosis less likely</td>
<td>+3</td>
</tr>
<tr>
<td>Hemoptysis</td>
<td>+1</td>
</tr>
<tr>
<td>Cancer</td>
<td>+1</td>
</tr>
</tbody>
</table>

*A score of less than 2 indicates low probability of PE, 2-6 intermediate probability, higher than 6 is high probability*

## INVESTIGATIONS

### DVT
- D-dimer → Rule out DVT in patient with low pretest probability
- Compression US → High sensitivity and specificity for DVT

### PE
- **CXR**
  - CXR can be normal in PE
  - Possible findings: atelectasis, effusion, elevated hemidiaphragm
  - Hampton hump: wedge-shaped density abutting the pleura
  - Westermark sign: avascularity distal to PE
- **ECG**
  - Sinus tachycardia or atrial fibrillation
  - Signs of RV strain → right axis deviation, p pulmonale, RBBB, S1Q3T3, T wave inversion in V1-V4
- **ABG** → Hypoxemia, hypocapnia, respiratory alkalosis, increase A-a gradient
- **D-dimer** → Rule out PE in patient with low pretest probability
- **CT angiography** → Se 90% and Sp 95%, PPV & NPV >95% if imaging concordant with clinical suspicion, < 80% if discordant
- **V/Q scan** → High Se (98%) and low Sp (10%). Sp improves to 97% for high probability VQ. Use when high pretest probability and CT scan not available/contraindicated. Can also exclude PE if low pretest prob, low prob VQ, 4% false negative.
- Lower extremity compression US

## MANAGEMENT

### ANTICOAGULATION – DVT AND PE
- **NOAC** (rivaroxaban, apixaban) preferred over warfarin. Can start alone or after 5 days of LMWH/UFH.
- **LMWH** (enoxaparin 1mg/kg SC q12h) preferred over IV UFH. Used as a bridge to long term anticoagulation – novel oral anticoagulant (NOAC) or warfarin
- **IV UFH** preferred when contemplating thrombolysis, indicated in renal failure, extreme obesity or high bleed risk
- Warfarin can be started at the same time as LMWH/UFH. Continue LMWH/UFH for minimum 5 days and INR >2.
- Fondaparinux, argatroban – use in HIT positive patients
- Duration of treatment

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69
- 1st proximal DVT, distal DVT or PE secondary to reversible cause → 3-6 months
- 1st unprovoked DVT/PE → at least 3 months then reassess benefit
- 2nd DVT/PE or malignancy → indefinite
  - Absolute contraindications – Neurosurgery, ocular surgery, intracranial bleeding within the past 10 days; active bleeding, severe bleeding diathesis, or platelets count < 20x10^3 /microliter

**SYSTEMIC THROMBOLYSIS**
- TPA 100mg over 2h
- Indications – Massive PE – PE + hemodynamic instability
**Blood Transfusions**

### BLOOD PRODUCTS AND INDICATIONS

#### PACKED RED BLOOD CELLS
- For acute blood loss or to increase O₂-carrying capacity if end organ ischemia
- Hb of < 70 g/L for patients who are hemodynamically stable, including those who are critically ill
- Hb < 80 g/L for patients with coronary ischemia

#### PLATELETS
- Platelet count < 10x10⁹/L
- Platelet count < 20x10⁹/L with infection or increased bleeding risk
- Platelet count < 50x10⁹/L with active bleeding or pre-procedure
- Contraindicated for those with TTP/HUS, HELLP, HIT

#### FRESH FROZEN PLASMA
- Contains all coagulation factors
- For bleeding or prior to a significant operative procedure in patients with INR, PT or PTT 1.8 times normal due to multiple factor deficiency when no coagulation factor concentrates or other alternative therapies are available (DIC, liver disease)
- For treatment of thrombotic thrombocytopenic purpura
- If available, prothrombin complex concentrates (PCCs)/Octaplex should be used for urgent reversal of warfarin therapy
- For those with an INR > 2 pre-procedure

#### CRYOPRECIPITATE
- Enriched for fibrinogen, von Willebrand Factor (vWF), factor VIII, and factor XIII.
- For bleeding with fibrinogen < 1 g/L, massive hemorrhage with fibrinogen < 1.5-2.0 g/L, acute phase of acute promyelocytic leukemia with fibrinogen < 1.5 g/L, intracranial hemorrhage secondary to treatment with tPA with fibrinogen < 2.0 g/L, bleeding in von Willebrand Diseases or Hemophilia A (when factor concentrates and DDAVP unavailable)

### TRANSFUSION COMPLICATIONS

#### Acute Hemolytic Reaction
- Pathophysiology: ABO incompatibility
- Symptoms: fever, hypotension, flank pain, hemoglobinuria, AKI within 24 hours
- Treatment: stop transfusion, IV fluids, diuretics, mannitol or dopamine

#### Delayed Hemolytic Reaction
- Pathophysiology: due to undetected allo-antibodies against minor antigens
- Symptoms: similar but less severe than acute hemolytic reaction within 5-7 days of transfusion
- Treatment: no specific treatment, important to note for future transfusions

#### Febrile non-hemolytic reaction
- Pathophysiology: recipient antibodies against donor WBC
- Symptoms: fevers, chills, rigors 0 – 6 hours post transfusion
- Treatment: acetaminophen ± meperidine

#### Allergic reaction
- Pathophysiology: recipient IgE against donor antigens
- Symptoms: urticaria
- Treatment: diphenhydramine

#### Anaphylactic reaction
- Pathophysiology: recipient antibodies against donor IgA
- Symptoms: bronchospasm, laryngeal edema, hypotension
- Treatment: stop transfusion, epinephrine, corticosteroids

**Transfusion-associated circulatory overload (TACO)**
- Pathophysiology: hypervolemia
- Symptoms: pulmonary edema, hypertension
- Treatment: stop transfusion, diuretics, O₂, nitrates, positive pressure ventilation, ensure slow transfusion rate on restarting

**Transfusion-related acute lung injury (TRALI)**
- Pathophysiology: donor antibody against recipient WBC which aggregate in pulmonary vasculature and release mediators, causing increased capillary permeability
- Symptoms: hypoxemia, pulmonary edema
- Treatment: stop transfusion, supportive measures

---

**References**
Infectious Disease

Approach to Fever of Unknown Origin

Fever of Unknown Origin

- Infection
  - TB
  - Abscess
  - Endocarditis
  - Osteomyelitis
  - Sinusitis
  - Lyme disease
  - Typhoid
  - CMV
  - EBV
  - Malaria

- Connective Tissue Disease
  - Giant cell arteritis
  - Lupus
  - Rheumatoid arthritis
  - Psoriatic arthritis
  - Reactive arthritis
  - Adult-onset Still’s

- Neoplasm
  - Lymphoma
  - Renal cell carcinoma
  - Hepatocellular carcinoma
  - Pancreatic cancer
  - Colon cancer
  - Sarcoma
  - Mastocytosis

- Other
  - Drugs
  - Factious
  - VTE
  - Thyroiditis, thyroid storm
  - Adrenal insufficiency
  - Pheochromocytoma

Definitions

✓ Fever of unknown origin (FUO) – fever on >1 occasion during ≥3 weeks and no diagnosis despite 1 week of investigations
Approach to Fever in a Returning Traveller

**FEVER IN A RETURNING TRAVELLER**

**DIFFERENTIAL DIAGNOSIS BASED ON REGION**
- Sub-Saharan Africa → Malaria >> dengue, rickettsial disease, enteric disease
- Southeast Asia → Dengue > malaria, enteric disease, Chikungunya
- Central and S. America → Enteric disease, malaria, dengue, Zika
- Caribbean and Mexico → Dengue >> Chikungunya > malaria,
- Middle East and S. Korea → Middle East Respiratory Syndrome

*The differential based on region of travel but should also include domestic infections, STIs and non-infectious causes*

**DIFFERENTIAL DIAGNOSIS BASED ON EXPOSURE**
- Unpurified drinking water → enteric disease, amebic liver abscess
- Freshwater swimming → Schistosomiasis, leptospirosis
- Animal bite → rabies
- African safari → Rickettsial disease, African trypanosomiasis
- Adult < 30 yo → Mononucleosis

**SYMPTOMS**
- Pre-travel preparation
- Travel itinerary
  - Dates of travel, region of travel, urban vs. rural, purpose of trip
- Exposure history
  - Street foods, untreated water, uncooked/unpasteurized dairy, body fluids, insect or animal bites
- Symptoms of common etiologies
  - Ebola → fever from an area with active transmission of Ebola within 21 days
  - Malaria → diarrhea, myalgias, cough, altered mental status
  - Dengue → headache, retro-orbital pain, severe myalgias, rash, petechiae
  - Chikungunya → joint pain, mild myalgias, fever
  - Typhoid → constipation, abdominal pain, possible rash, bradycardia
  - Rickettsial disease → headache, myalgias, lymphadenopathy, possible rash
  - Zika → fever, rash, arthralgias, headache, conjunctivitis

**INVESTIGATIONS**
- General Investigations
  - CBC w/ differential, electrolytes, LFTs, blood culture (malaria, S. typhi), urinalysis, rapid malaria test
- Other tests based on clinical presentation, exposure and region of travel
  - Ova and parasite exam
  - Blood smear
  - Infectious serologies – anti-dengue IgM
  - STI and HIV testing
  - Tuberculin skin test
  - Bone marrow aspirate and CSF studies
  - Biopsy of lymph nodes or skin lesions

**ADDITIONAL INFORMATION – TREATMENT OF COMMON ETIOLOGIES**
- Malaria → artesunate + malarone + doxycycline
- Dengue → acetaminophen, avoid NSAIDs
- Typhoid → quinolone antibiotic + ceftriaxone
- Zika → rest, fluids, acetaminophen, condom use, avoid pregnancy
## Endocarditis

### Definitions
- **Infection of the endothelium of heart, including the cardiac valves**
- **Acute bacterial endocarditis (ABE)**
  - Syndrome presents as acute fulminant infection due to a highly virulent and invasive organism – *S. aureus*, *S. pneumonia*, β-hemolytic strep
- **Subacute bacterial endocarditis (SBE)**
  - Infection with less virulent organism – *S. viridans*, enterococcus, *S. epidermidis*, GNR

### Risk Factors
- Prior endocarditis, rheumatic heart disease, other acquired valvular lesions (AS, AR, MR, mitral valve prolapse), hypertrophic cardiomyopathy, IV drug use, indwelling venous catheters, poor dentition, systemic disease – hemodialysis, diabetes mellitus, prosthetic material in the heart

### Symptoms
- General – fever, rigors, night sweats, anorexia, weight loss, fatigue
- Cardiac – dyspnea, chest pain
- Embolic – stroke, PE, MI mycotic aneurysm
- Immune complex – arthritis, glomerulonephritis

### Signs
- General – fever, change in mental status, splinter hemorrhages, petechiae
- Cardiac – regurgitant murmur, signs of CHF
- HEENT – Roth spots (retinal hemorrhage and pale center), palatal or conjunctival petechiae
- Embolic – Janeway lesions (non-tender septic embolic hemorrhagic, macules on palms/soles)
- Immune complex – Osler’s noes (tender immune complexes nodules on the pads of the digits)

### Investigations
- Bloodwork: CBC w/ differential, ESR, RF, BUN, Cr – Increased WBC in ABE and anemia in SBE
- Blood cultures
  - 3 sets (aerobic and anaerobic bottles) from different sites, spaced 1 hour apart
  - 2 sets after antibiotics have been initiated repeated every 24-48h until negative
- Urinalysis and culture
- ECG – on admission and at regular intervals to assess for conduction abnormalities
- Echocardiogram and consider brain MRI if suspect silent cerebral emboli

### Management

#### Diagnosis – Modified Duke’s Criteria

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture positive from two separate cultures</td>
<td>Predisposing condition</td>
</tr>
<tr>
<td>Single positive culture from <em>Coxiella burnetii</em></td>
<td>Fever (≥38°C)</td>
</tr>
<tr>
<td>Endocardial involvement</td>
<td>Vascular phenomena – Septic arterial or pulmonary emboli, Mycotic aneurysms, Intracranial hemorrhage, Janeway lesions</td>
</tr>
<tr>
<td>Echocardiogram with vegetation, abscess or prosthetic dehiscence</td>
<td>Immunologic phenomena – Roth spots, Osler’s nodes, Positive rheumatoid factor, Glomerulonephritis</td>
</tr>
<tr>
<td>New valvular regurgitation</td>
<td>Blood cultures not meeting major criteria</td>
</tr>
</tbody>
</table>

*Definitive (i.e. highly probable): 2 major OR 1 major + 3 minor OR 5 minor*

*Possible: 1 major + 1 minor OR 3 minor*
<table>
<thead>
<tr>
<th>TREATMENT</th>
</tr>
</thead>
</table>
| • Empiric Antibiotic Therapy  
  o Native valve endocarditis – IV Vancomycin and IV Ceftriaxone  
  o Prosthetic valve endocarditis – IV Vancomycin + IV Ceftriaxone + IV Gentamycin  
  o Narrow treatment based on cultures  
  o Duration of antibiotic treatment usually 4-6 weeks  
| • Fever can persist for over 1 week after antibiotic treatment started. If longer than 1 week consider metastatic infection.  
| • Systemic anticoagulation is relative contraindication due to risk of hemorrhage with cerebral emboli  
| • Monitor for complications – CHF, conduction block, new emboli  
| • Surgical valvular replacement indicated if:  
  o Severe valvular dysfunction causing refractory CHF  
  o Uncontrolled infection despite antibiotics  
  o Infection with fungal organisms  
  o Systemic emboli  
  o Prosthetic valve endocarditis  |
**Meningitis**

**ETIOLOGY**
- **Bacterial** – *S. pneumoniae* (30-60%), *N. meningitidis* (10-35%), *H. influenzae* (<5%), *L. monocytogenes* (5-10%), Gram negative rods (1-10%)
- **Viral** – HSV, VZV, enteroviruses
- **Fungal** – *Cryptococcus* (in severely immunosuppressed)
- **Other** – Lyme disease, neurosyphilis, TB

**SYMPTOMS**
- Fever, headache, stiff neck, photosensitivity, seizures, change in mental status
- Note: elderly patients present atypically and may present with lethargy and no fever

**SIGNS**
- **Vitals** – fever, tachycardia
- **Signs of meningeal irritation**
  - Nuchal rigidity, jolt sensitivity
  - Kernig’s sign – position patient with hips and knees flexed at 90°, positive if rigidity with passive extension of knees
  - Brudzinski’s sign – position patient supine with legs supine, positive if passive flexion of the neck causes involuntary hip and/or knee flexion
- **Focal neurological findings** – hemiparesis, aphasia, visual field cuts, CN palsies
- **Funduscopic findings** – papilledema, absent venous pulsations
- **HEENT findings** – sinus tenderness, clear rhinorrhea (CSF leak)
- **Skin findings** – petechial rash (*N. meningitidis*), genital or oral ulcers (HSV)

**MANAGEMENT**
- **Droplet precautions**
- **Stat blood cultures then begin immediate antibiotic therapy + corticosteroids**
  - Two blood culture samples before antibiotics
  - Corticosteroids – Dexamethasone 10mg IV q6h x 4 days
  - Begin empiric antibiotics
    - i. Ceftriaxone 2g IV q12h + Vancomycin 15-20mg/kg IV q12h
    - ii. If >50yo or alcoholic add ampicillin 2g IV q4h for *Listeria*
    - iii. Immunosuppressed – ampicillin + ceftazidime + vancomycin
- **CT head (if indicated)**
  - Indications (≥1 high risk feature):
    - i. >60 yo
    - ii. Immunosuppressed
    - iii. History of CNS disease (mass lesion, stroke, or focal infection)
    - iv. New-onset seizure
    - v. Change in mental status
    - vi. Focal neurological findings
    - vii. Papilledema
- **LP (if not contraindicated)**
  - Contraindications
    - i. Mass lesion causing increased ICP
    - ii. Infection over LP site
    - iii. Suspected epidural abscess
iv. Platelets <50, high INR or aPTT
v. Uncooperative patient

### CSF Findings in Meningitis

<table>
<thead>
<tr>
<th>Type</th>
<th>Appearance</th>
<th>Pressure (cm H2O)</th>
<th>WBC/mm³ (predeominant type)</th>
<th>Glucose (mg/dL)</th>
<th>Total Protein (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>Clear</td>
<td>9-18</td>
<td>0-5 (lymphocytes)</td>
<td>50-75</td>
<td>15-40</td>
</tr>
<tr>
<td>Bacterial</td>
<td>Cloudy</td>
<td>18-30</td>
<td>100 – 10,000 (neutrophils)</td>
<td>&lt;45</td>
<td>100-1000</td>
</tr>
<tr>
<td>TB</td>
<td>Cloudy</td>
<td>18-30</td>
<td>&lt;500 (lymphocytes)</td>
<td>&lt;45</td>
<td>100-200</td>
</tr>
<tr>
<td>Fungal</td>
<td>Cloudy</td>
<td>18-30</td>
<td>&lt;300 (lymphocytes)</td>
<td>&lt;45</td>
<td>40-300</td>
</tr>
<tr>
<td>Aseptic</td>
<td>Clear</td>
<td>9-18</td>
<td>&lt;300 (lymphocytes)</td>
<td>50-100</td>
<td>50-100</td>
</tr>
</tbody>
</table>
Tuberculosis

**TUBERCULOSIS**

**PATHOPHYSIOLOGY**
- Inhalation of aerosol droplets containing *Mycobacterium Tuberculosis* with subsequent deposition in lungs which results in one of four possible outcomes:
  - Immediate clearance of the organism
  - Primary disease – immediate onset of active disease
  - Latent infection
  - Reactivation disease – onset of active disease many years following a period of latent infection

Reactivation disease occurs in 5-10 % of healthy individuals, risk increases with HIV and other medical conditions.

**RISK FACTORS**

<table>
<thead>
<tr>
<th>High prevalence populations – more likely to be exposed and infected</th>
<th>High risk populations – infected patients that are more likely to progress to active disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immigrants from high-prevalence area</td>
<td>HIV positive</td>
</tr>
<tr>
<td>Indigenous population</td>
<td>Immunosuppressed (biologics, uncontrolled diabetes, smoking)</td>
</tr>
<tr>
<td>Homeless</td>
<td>Close contact with patients with TB</td>
</tr>
<tr>
<td>IV drug use</td>
<td>Underweight</td>
</tr>
<tr>
<td>Medically underserved</td>
<td>CKD</td>
</tr>
<tr>
<td>Resident or worker in jail or long-term facility</td>
<td>Organ transplant</td>
</tr>
<tr>
<td>Close contact with patients with TB</td>
<td>IV use</td>
</tr>
<tr>
<td></td>
<td>Alcohol</td>
</tr>
<tr>
<td></td>
<td>Malnourishment</td>
</tr>
<tr>
<td></td>
<td>Cancer</td>
</tr>
<tr>
<td></td>
<td>Gastrectomy</td>
</tr>
</tbody>
</table>

**SYMPTOMS**

**LATENT TB**
- Asymptomatic

**PRIMARY PULMONARY AND REACTIVATION OF TB**
- General: Fever, night sweats, anorexia, weight loss, fatigue
- Pulmonary: Pleuritic chest pain, chronic cough and hemoptysis

**REACTIVATION - EXTRAPULMONARY**
- Lymphadenitis, pericarditis, peritonitis, meningitis, nephritis, osteomyelitis (vertebral = Pott’s disease), hepatitis, splenitis, cutaneous, arthritis

**SIGNS**
- Fever, malaise and abnormal respiratory exam in pulmonary TB

**MANAGEMENT**

**GENERAL**
- All patients with suspected TB should have CXR
  - Primary TB → middle or lower lobe consolidation +/- effusion +/- cavitation
  - Reactivation pulmonary TB → apical infiltrate +/- volume loss +/- cavitation
- Bloodwork: CBC, lytes, urea, Cr, AST, ALT, ALP, bilirubin, albumin, urinalysis, HIV serology

**LATENT TB**
- Tuberculin Skin Test (TST)
  - The following cutoffs are considered positive for the corresponding populations:
    - ≥5 mm – HIV positive, recent TB contact, CXR signs, prior TB
| ≥10 mm – other risk factors |
| ≥15 mm – no risk factors |

- Interferon Gamma Release Assays – evaluate latent TB in those with previous BCG vaccination
- Treatment: Isoniazid + pyridoxine for 9 months OR rifampin for 4 months

## ACTIVE TB

- Isolate patient with airborne precautions
- Blood culture and screen, urine culture and screen
- Acid Fast Bacilli (AFB) smear and culture of sputum
- PCR on non-bloody sputum for rapid diagnosis and detection of isoniazid resistance
- Thoracentesis if effusion – send fluid for AFB and TB culture
- Treatment: Rifampin, Isoniazid, Pyrazinamide, Ethambutol (RIPE) for 2 months followed by isoniazid + rifampin for 4 months
- Monitor for adverse drug reactions:
  - Isoniazid – hepatotoxicity, peripheral neuropathy (need to take pyridoxine)
  - Rifampin - hepatotoxicity, orange-red discoloration of body fluids
  - Ethambutol – optic neuropathy
  - Pyrazinamide – hepatotoxicity, polyarthralgias
- Obtain monthly smears/cultures on treatment until 2 consecutive tests are negative
# C. Difficle Infection

## C. DIFFICILE

### PATHOPHYSIOLOGY

- Ingestion of *C. diff* spores leading to colonization in the colonic flora
- *C. diff* proliferates when there is a disruption in the colonic flora by antibiotics or chemotherapy
- *C. diff* releases toxin A/B -> colonic mucosal inflammation and necrosis -> pseudomembranous colitis

### RISK FACTORS

- Associated with all antibiotic use especially B-lactams, clindamycin and quinolones
- Elderly
- Nursing home residents
- IBD
- PPI use

### SYMPTOMS

- Asymptomatic in <3% of healthy adults
- Acute watery diarrhea +/-blood +/- mucous with lower abdominal pain

### SIGNS

- Fever, signs of hypovolemia from diarrhea
- Complications
  - Pseudomembranous colitis – bowel wall thickening
  - Fulminant colitis in 2-3% – toxic megacolon or bowel perforation – systemic toxicity

### INVESTIGATION

- CBC – significantly elevated WBC
- Stool Enzyme immunoassay (EIA) – detects toxin A or B
- Stool PCR for *C. diff*
- Abdominal x-ray
- Consider flex sigmoidoscopy if uncertain diagnosis and no improvement with treatment

### MANAGEMENT

- Contact precautions (gloves and gown when entering patient room), private room and dedicated toilet, hand hygiene
- Discontinue inciting antibiotic as soon as possible
- Non-severe infection
  - First line tx: Vancomycin 125mg po q6h or Fidaxomicin 200 mg po twice daily x10-14 days
  - Second line tx: flagyl 500mg po q8h x10-14days
- Severe infection - >12 BM/day, T >39°C, WBC >25, hypotension, ICU care, ileus
  - Vancomycin 125mg po q6h and flagyl 500mg IV q8h
  - If ileus is present, Vancomycin can be given per rectum
- Worsening infection despite antibiotics – ileus, increasing WBC, increasing lactate, shock, toxic megacolon or peritonitis
  - Abdominal CT and surgical consultation for possible colectomy
- Recurrent infection
  - 1st recurrence – vancomycin 125mg po q6h x10-14 days
  - Subsequent recurrence – vancomycin PO pulse therapy and taper
  - Fecal microbiota transplant if multiple recurrences of C diff infection
# HIV

## PATHOPHYSIOLOGY

- HIV – Retrovirus uses the host genome to replicate. As HIV viral load increases, the host’s CD4 immune cells will decrease leading to progressive immune system dysfunction which predisposes patients to opportunistic infections and malignancies
- AIDS – HIV and CD4 < 200/mm$^3$

## TRANSMISSION

- Sexual contact – homosexual, heterosexual
- Parenteral – IV drug use, unsafe needle use, health workers, transfusion (rare)
- Maternal-fetal – in utero, delivery, breast feeding

## DISEASE COURSE

### Acute retroviral syndrome – 2-6 weeks after infection lasting 10-15 days

- Acute febrile “mononucleosis like” illness, lymphadenopathy, pharyngitis, rash, headache, arthralgias, myalgias, GI symptoms, oral ulcers

### Asymptomatic latent stage

- HIV infects and replicates in the CD4+ T lymphocytes

### Symptomatic stage – secondary to opportunistic infections or malignancies due to low CD4 count

- **CD4 <500**
  - Constitutional symptoms
  - Cutaneous
    - Kaposi’s sarcoma – red-purple non-blanching nodular lesions
    - Seborrheic dermatitis – eosinophilic folliculitis
    - Herpes simplex virus (HSV) – warts
  - Oral
    - Oral hairy leukoplakia – painless white coating on lateral tongue
    - Candidiasis (thrush) – curd-like patches with burning or pain
  - Hematological
    - Lymphoma
  - Infectious
    - Varicella zoster virus (VZV)
    - TB
    - Neurosyphilis – meningitis, cranial nerve palsies, dementia, otic or optho s/s

- **CD4 <200**
  - Pulmonary
    - *Pneumocystis jiroveci* (PCP) – fever, night sweats, dyspnea on exertion, non-productive cough
  - Cutaneous
    - *Bartonella* – friable violaceous vascular papules
  - Neurological
    - *Toxoplasmosis* – enhancing lesions in the basal ganglia presenting with change in mental status and focal neurological deficits
    - *Coccidiomycosis* – meningitis
  - GI
    - *Histoplasmosis* - GI bleeding

- **CD4 <50-100**
  - CMV – retinitis, esophagitis, colitis, hepatitis, neuropathies, encephalitis
  - Mycobacterium avium complex (MAC) – fever, night sweats, weight loss, diarrhea, pancytopenia
- Cryptococcal meningitis
- Progressive multifocal leukoencephalopathy (PML) – multiple non-enhancing lesions in the white matter
- CNS Lymphoma – enhancing ring lesion
- Invasive aspergillosis – cavitary lesions in the lungs
- Bacillary angiomatosis (disseminated *Bartonella*) – friable violaceous vascular lesions
- **Note: CD4 <50 is a medical emergency!**

### INVESTIGATIONS

### DIAGNOSIS
- ELISA for HIV1 Ab/Ag - positive 1-12 weeks after infection
- Rapid tests/Ab test – low PPV, needs confirmation
- PCR for HIV1 RNA in plasma – viral loads

### NEWLY DIAGNOSED HIV
- CD4, PCR, HIV genotype
- CBC w/diff., Cr, electrolyes, LFTs, A1C, fasting lipids
- Tuberculin skin test
- Syphilis screen, toxoplasmosis screen, CMV IgG, hepatitis A, B and C serologies, chlamydia & gonorrhea screen
- Baseline CXR, pap smear and anal pap

### MANAGEMENT
- Counselling of treatment options, adherence, and disclosure
- Antiretroviral therapy – 2 NRTIs and either integrase inhibitor or protease inhibitor
  - Nucleoside/tide reverse transcriptase inhibitor (NRTI)
    - Abacavir, Emtricitabine, Lamivudine, Tenofovir, Zidovudine
  - Nonnucleoside reverse transcriptase inhibitor (NNRTI)
    - Efavirenz, Etravirine, Nevirapine, Rilpivirine
  - Protease inhibitor (PI)
    - Atazanavir, Darunavir, Lopinavir, Ritonavir
  - Fusion inhibitor – enfuvirtide
  - Entry inhibitor (CCR5 antagonist) – maraviroc
  - Integrase inhibitor – raltegravir
- Opportunistic Infections prophylaxis
  - PJP prophylaxis when CD4<200 – TMP-SMX
  - Toxoplasmosis prophylaxis when CD4 <100– TMP-SMX
  - MAC prophylaxis when CD4 <50 – Azithromycin
# Cellulitis

## Background
- Infection involving the dermis and subcutaneous tissue
- Most common pathogens: Staphylococci, MRSA or Streptococcus

## Symptoms and Signs
- Swollen, erythematous, painful, hot plaque with poorly defined borders
- MRSA risk factors: hospitalization, street involvement, IV drug use, athletes
- Patients with diabetes are at increased risk due to peripheral neuropathy leading to decreased sensation if cellulitis present and peripheral vascular disease impairing healing if cellulitis develops

## Management
- Antibiotics
  - Mild cellulitis – cephalexin 500mg po qid for 5 – 14 days
  - Systemic toxicity or severe cellulitis – cefazolin 1-2g IV q4-6h for 7 – 14 days
- If MRSA suspected add Vancomycin
- Incision and drainage if abscess present
- Wound care may be required in patients with diabetes who develop cellulitis

## Isolation Modalities

### Airborne
- Negative pressure room with high-efficiency particulate aerator filter
- Certified N95 mask
- Indications – varicella, tuberculosis, measles

### Droplet
- Mask within 3-6ft, eye protection
- Indications – H. influenza, N. meningitidis, influenza, RSK, pertussis, parainfluenza, etc.

### Contact
- Glove, gown, wash hands
- Indications – C. difficle, VRE, MRSA, carbapenem-resistant organisms, ESBL

## Drug Resistance Organisms

### Background
- Antibiotic resistance occurs when bacteria change in response to use of antibiotics such that the organisms do not respond to the antibiotic treatment
- Antibiotic resistance is leading to longer hospital stays, higher medical costs and increased mortality

### Factors Leading to Emergence of Resistance
- Societal pressures – even when used appropriately causes a selective pressure for resistant organisms
- Inappropriate use or inadequate diagnosis – use of anti-biotics for a non-bacterial infection
- Agricultural use – adding antibiotics to agriculture feed

## References
**NEPHROLOGY**

**Approach to Acid-Base Disturbances**

**DEFINITIONS**

- **Normal values**
  - pH: 7.35–7.45
  - pCO₂: 22 – 30 mEq/L
  - HCO₃: 36 – 44mMg
- **Acidemia**: pH <7.36, **Acidosis**: process of increasing H⁺ concentration
- **Alkalemia**: pH > 7.44, **Alkalosis**: process of decreasing H⁺ concentration
- **Anion gap** = [Na⁺] – ([HCO₃] + [Cl⁻])
  - Normal: 10–14 mEq/L
- **Osmolar gap** = (2 x [Na⁺] + [urea] + [glucose])
  - Normal: OG >10

**APPROACH TO ACID-BASE DISTURBANCES**

**GENERAL**

1. **Determine the primary disorder based on pH, HCO₃ and PₐCO₂**

<table>
<thead>
<tr>
<th>Primary disorder</th>
<th>Problem</th>
<th>pH</th>
<th>HCO₃</th>
<th>PₐCO₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic acidosis</td>
<td>Gain H⁺ or lose HCO₃</td>
<td>Decrease</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
<tr>
<td>Metabolic alkalosis</td>
<td>Gain HCO₃ or lose H⁺</td>
<td>Increase</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Respiratory acidosis</td>
<td>Hypoventilation</td>
<td>Decrease</td>
<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Respiratory alkalosis</td>
<td>Hyperventilation</td>
<td>Increase</td>
<td>Decrease</td>
<td>Decrease</td>
</tr>
</tbody>
</table>

*Metabolic disorders of HCO₃ and CO₂ changes are to compensate and maintain the pH in normal range. Respiratory acidosis and alkalosis are changes in CO₂ and HCO₃ changes are to compensate and maintain pH in normal range.*

2. **Determine if compensation for the primary disorder**

   a. Metabolic acidosis – Decrease 1 HCO₃ → Decrease 1 CO₂
   b. Metabolic alkalosis – Increase 10 HCO₃ → Increase 5-7 CO₂
   c. Respiratory acidosis – Acute: Increase 10 CO₂ → Increase 1 HCO₃ and Chronic: Increase 10 CO₂ → Increase 3 HCO₃
   d. Respiratory alkalosis – Acute: Decrease 10 CO₂ → Decrease 2 HCO₃ and Chronic: Decrease 10 CO₂ → Decrease 5 HCO₃

*Respiratory compensation for metabolic disturbances occurs in minutes. Renal compensation for respiratory disturbances occurs in hours to days. If compensation is not complete or pH is fully normal consider mixed disorder.*

3. **Calculate anion gap**

   a. Increase in AG < decrease in HCO₃ consider co-existing non-AG metabolic acidosis
   b. Increase in AG > decrease in HCO₃ consider co-existing metabolic alkalosis

4. **Calculate osmolar gap**

   a. OG > 10 consider methanol poisoning, ethylene glycol

**METABOLIC ACIDOSIS**

1. **Recognize the symptoms and signs of metabolic acidosis**
   a. Hypoventilation with increased respiratory rate is a sign of respiratory compensation
2. **Calculate AG to determine if anion gap metabolic acidosis versus non-anion gap metabolic acidosis**
3. **If AG metabolic acidosis proceed to determining presence of ketones, lactate, uric acid, osmole gap and tox screening as indicated**
   a. + ketones → DKA, starvation
   b. – ketones and + lactate → lactic acidosis
c. – ketones and uremia → renal failure
d. – ketones, + tox, OG < 10 → salicylates, 5-oxoprolinuria
e. – ketones, + tox, OG > 10 → ethanol, methanol, ethylene glycol, propylene glycol, 5-oxoprolinuria

4. If non-AG metabolic acidosis proceed to determining urine anion gap (UAG = $U_{\text{Na}} + U_{\text{K}} - U_{\text{Cl}}$), urine pH, fractional excretion of $\text{HCO}_3^-$ and serum potassium
   a. + UAG → renal cause including renal failure or renal tubular acidosis
   b. – UAG → GI, dilatational, posthypocapnia

5. Treatment of metabolic acidosis
   a. Treat the cause
      i. DKA → fluid resuscitation and insulin
      ii. Type A lactic acidosis → restore tissue perfusion
      iii. Methanol and ethylene glycol poisoning → ethanol/fomepizole +/- dialysis
      iv. ASA overdose → alkaline diuresis +/- dialysis
   b. Alkali therapy – $\text{NaHCO}_3$ 50mmol in 1L D5W x3
      i. Goal: serum $\text{HCO}_3^>$8 and pH > 7.2
      ii. CAUTION: risk of volume overload, overshoot alkalosis and hypokalemia

6. Etiology – AG metabolic acidosis – MUDPILES CT – Methanol, uremia, diabetic ketoacidosis, paraldehyde, isopropyl alcohol/iron/ibuprofen/indomethacin, lactic acidosis, ethylene glycol, salicylates, cyanide/CO, alcoholic ketoacidosis, toluene

7. Etiology – Non-AG metabolic acidosis – GI loses (diarrhea, intestinal fistula, pancreatic fistula), renal, dilatational (IV fluids), post-hypocapnia, ingestions (acetazolamide, cholestyramine, toluene)

### METABOLIC ACIDOSIS

<table>
<thead>
<tr>
<th>1. Determine if saline-responsive or saline-resistant metabolic alkalosis based on Urine Cl concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. $U_{\text{Cl}} &lt; 20 \text{ mEq/L}$ → saline-responsive</td>
</tr>
<tr>
<td>b. $U_{\text{Cl}} &gt; 20 \text{ mEq/L}$ → saline-resistant</td>
</tr>
<tr>
<td>2. If saline-resistant determine volume status – hypertensive versus hypotensive or normotensive</td>
</tr>
<tr>
<td>3. Treatment of metabolic alkalosis</td>
</tr>
<tr>
<td>a. Saline-responsive → volume repletion with NS +/- carbonic anhydrase inhibitors which facilitate $\text{HCO}_3^-$ secretion in urine</td>
</tr>
<tr>
<td>b. Saline-resistant → remove source of aldosterone or glucocorticoid +/- spironolactone</td>
</tr>
<tr>
<td>4. Etiology – GI losses, prior diuretics, post-hypercapnia, laxatives, primary or secondary hyperaldosteronism, severe hypokalemia, exogenous alkali, Bartter syndrome, Gitelman’s syndrome</td>
</tr>
</tbody>
</table>

### APPROACH TO RESPIRATORY ACIDOSIS

| 1. Hypoventilation and decreased LOC are red flags |
| 2. Identify cause of hypoventilation leading to respiratory acidosis |
| 3. Treatment of respiratory acidosis |
| a. Respiratory support with mechanical ventilation to improve gas exchange, relieve respiratory distress and protect airway |
| 4. Etiology – CNS depression (sedatives, CNS trauma, chronic hypercapnia, central sleep apnea), neuromuscular disorders, (GBS, MG, polio, ALS), upper and lower airway abnormalities |

### APPROACH TO RESPIRATORY ALKALOSIS

| 1. Identify the signs and symptoms |
| a. Hyperventilation +/- hypoxia |
| 2. Identify the cause of hyperventilation leading to respiratory alkalosis |
| 3. Etiology – hypoxia leading to hyperventilation (pneumonia, pulmonary edema, PE), primary hyperventilation (pain, anxiety, trauma, stroke, drugs, pregnancy, sepsis), pseudorespiratory alkalosis (decreased perfusion to lungs with preserved ventilation) |
Approach to Glomerular Disease

Glomerular Disease

Nephritic Syndrome

- Anti-GBM mediated (rapidly progressive GN type 1)
  - Positive anti-GBM
    - Goodpasture’s disease – lung hemorrhage
    - Anti-GBM disease - no lung hemorrhage

Immune complex mediated (rapidly progressive GN Type 2)

- Normal C3
  - IgA nephropathy
  - Henoch-Schoniein pupura

- Decreased C3
  - Membranoproliferative
  - SLE
  - Infective endocarditis
  - Post-infectious GN
  - Cryoglobulinemia

Nephrotic Syndrome

- Non-immune mediated – rapidly progressive GN Type 3
  - Positive ANCA
    - Granulomatosis with polyangitis
    - Eosinophilic granulomatosis
    - Microscopic polyangitis

- Decreased C3
  - Minimal change disease
  - Membranous
  - Glomerulonephritis
  - Focal segmental glomerulosclerosis
  - Membrano-proliferative

Primary glomerular disease

- Diabetic nephropathy
- Amyloidosis
- SLE
- Cryoglobuliniemia
- HIV
- Drugs associated (NSAIDs, gold, pamidronate)

Systemic disease with glomerular involvement
GLOMERULAR DISEASE

DEFINITIONS

- Nephrotic syndrome
  - Pathologically: abnormal glomerular podocyte permeability to protein
  - Clinically: proteinuria >3.5 g/d, albumin < 35 g/L, edema, dyslipidemia, hypertension, thrombosis

- Glomerulonephritis/ Nephritic syndrome
  - Pathologically: intraglomerular inflammation which can be focal or diffuse
  - Clinically: hematuria with dysmorphic RBCs or RBC casts, may have subnephrotic proteinuria often with AKI, HTN, edema
  - Acute GN progresses in days, rapidly progressive GN (RPGN) progresses over weeks, chronic GN occurs over months and may not progress, may simply have asymptomatic hematuria

ADDITIONAL INFORMATION

INVESTIGATIONS

NEPHROTIC SYNDROME

- Bloodwork – CBC, electrolytes, urea, Cr, albumin, lipids (Low serum albumin and high serum lipids)
- Urinalysis – hyaline casts, lipid droplets (oval fat bodies)
- Measure proteinuria – 24h urine collection, urine albumin/Cr ration and protein/Cr ratio (proteinuria >3.5g/d)
- Investigate for secondary causes
  - Increased HbA1C + retinopathy -> suggests diabetic nephropathy likely
  - ANA, anti-dsDNA, C3/C4 – autoimmune causes
  - Serum protein electrophoresis, urine protein electrophoresis, HIV serology

NEPHRITIC SYNDROME

- Bloodwork – CBC, electrolytes, urea, Cr, Ck, uric acid (Increased Cr and urea)
- Urinalysis – RBC casts, dysmorphic RBCs, hematuria
- Investigate for secondary causes
  - Anti-GBM – positive in anti-GBM mediated GN
  - ANA, anti dsDNA, ENA, p ANCA, c ANCA – positive in non-immune mediated GN
  - C3, C4 – complements low in immune complex mediated GN except for IGA nephropathy
  - ASO titer – post-streptococcal GN
  - HBV, HCV serology
  - Cryoglobulin – positive in cryoglobulinemia
- Quantitative Ig, serum protein electrophoresis

ADDITIONAL INVESTIGATIONS

- Renal Ultrasound or CT – Rule out obstruction and evaluate kidney size and hydronephrosis
- Renal biopsy

MANAGEMENT

NEPHROTIC SYNDROME

- General – Sodium restriction, protein supplements, diuretics for edema, treat hyperlipidemia, BP control
- ACE inhibitor or ARB - Decrease proteinuria and slow progression of renal disease –
- Primary glomerular disease – Steroids or cyclophosphamide
- Anticoagulation if high risk for thrombosis

NEPHRITIC SYNDROME

- Acute GN – methylprednisone IV for 3 days
- SLE GN – steroids and cyclophosphamides
- ANCA + GN or anti-GBM GN – pulse steroids and cyclophosphamides +/- plasma exchange
Approach to Hypokalemia

**HYPOKALEMIA**

**SYMPTOMS**
- Asymptomatic when mild (3.0 – 3.5 mmol/L)
- Muscular – Weakness, paralysis, cramps, paresthesia, tetany, muscle tenderness
- Renal – Nocturia, polydipsia, polyuria

**SIGNS**
- ECG changes – U waves, flat or inverted T waves, increased QT interval, PVCs, VT, VF

**MANAGEMENT**
- Potassium repletion: 10 mmol K increases serum K 0.1 mmol/L
- KCl 40 mmol PO q4-h if nonurgent, KCl 10 mmol/h IV if urgent
- Beware of excessive potassium repletion if transcellular shift cause of hypokalemia
- Replete low magnesium
Approach to Hyperkalemia

**Symptoms**
- Asymptomatic when mild
- General – nausea, hypoventilation
- Muscular – Weakness, stiffness, ascending paralysis, paresthesia
- Cardiac – palpitations

**Signs**
- ECG changes – peaked Ts > widened QRS > increased PR interval > wide and flat P wave > sine wave > VF/PEA

**Management**
- Emergent treatment if $K^+ > 6.0$ and/or ECG and/or symptoms
  - Calcium gluconate 1-2 amps IV – cardiac stabilization
- Shift K into cells (temporary measure)
  - Regular insulin 10 U IV, need to order 1 amp D50W and glucscans q1h x 4
  - Sodium bicarbonate 1 amp IV
- Excrete K
  - Insert foley catheter to monitor urine output
  - If hypovolemic give IV Normal Saline
  - If hypervolemic give IV Furosemide
  - If no urine output despite treatment, then consider hemodialysis
Approach to Hyponatremia

HYPONATREMIA
- Excess water relative to Na. Almost always due to high ADH.

SYMPTOMS
- Acute hyponatremia (24h – 48h) likely to be symptomatic. Chronic (>24h – 48h) more likely to be asymptomatic.
- Neurological symptoms → headache, nausea, malaise, lethargy, weakness, muscle cramps, anorexia, somnolence, personality changes. Complications → seizure, coma, respiratory arrest, brain damage, brain herniation, death.

MANAGEMENT
- Depends on volume status, acuity and symptoms
  - If acute symptomatic, rapid correction of Na – 2mEq/L/h with hypertonic saline for the first 2-3h until symptoms resolve
  - If chronic symptomatic, correct Na by no more than 0.5 mEq/L/h and no more than 8 mEq/24 hr
  - If severe (Na<120) and neurological symptoms can administer 3% NaCl and dDAVP to prevent overcorrection
  - Rate of Na correction should NOT exceed 8 mEq/L/24 hours due to risk of irreversible osmotic demyelination syndrome
- Hypovolemic hyponatremia → volume repletion with NS at a slow rate
- SIADH → free water restriction and treat underlying cause → salt tablets → consider hypertonic saline if symptoms fail to resolve or Na fails to increase with water restriction
- Hypervolemic hyponatremia → free water restriction

ADDITIONAL INFORMATION
SIADH: Inappropriate ADH secretion leading to hyponatremia
Malignancy – lung, brain, GI, GU
Pulmonary – pneumonia, TB, aspergillosis
Intracranial – trauma, stroke, subarachnoid hemorrhage
Drugs – antipsychotics, antidepressants
Other – pain, nausea, post-operative state
Approach to Hypernatremia

**HYPERNATREMIA**
- Free water deficit relative to total body Na, due to loss of hypotonic fluid AND impaired access to free water.

**SYMPTOMS**
- Polyuria, thirst, confusion, decreased level of consciousness, coma

**MANAGEMENT**
- Restore access to water or replace free water deficit with D5W
- Rate of Na decrease should not exceed 0.5 mEq/L/h to avoid cerebral edema
- Central DI → dDAVP
- Nephrogenic DI → treat cause, Na restriction + thiazide diuretic

**ADDITIONAL INFORMATION**

**DIABETES INSIPIDUS**
- Central DI – defect in central release of ADH
  - DDx: Neurosurgery, granulomatous disease, trauma, vascular events, malignancy
  - Diagnosed by $U_{\text{o}} < 300$ which rises after administering DDAVP
- Nephrogenic DI – impaired renal response to ADH
  - Lithium, hypokalemia, hypercalcemia and congenital
  - Diagnosed when DDAVP fails to concentrate urine

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Approach to Hypocalcemia

HYPOCALCEMIA
- Total calcium is influenced by binding protein albumin and calcium must be corrected for this
- Corrected Ca\(^{2+}\) = measured Ca + 0.02(40 - albumin)
  - For every decrease in albumin by 10 from 40, increase Ca by 0.2

SYMPTOMS
- Neuromuscular irritability → perioral paresthesia, cramps, Trousseau sign (inflation of BP cuff for 3 minutes causes carpal spasm) and Chvostek's sign (tapping facial nerve causes contraction of facial muscles), increased ICP, seizures
- MSK → bone pain, muscle weakness
- Psychiatric → psychosis, irritability, depression
- Cardiac → prolonged QT

MANAGEMENT
- If symptomatic → Ca gluconate (1-2 g IV over 20 min), oral Ca, calcitriol
- If chronic → oral Ca, calcitriol, vitamin D supplementation
- Consider thiazide diuretic to decrease Ca excretion in urine
Approach to Hypercalcemia

Hypercalcemia (Ca>2.6 mmol/L)

Determine PTH

Low PTH → determine PO4

High/Normal PTH

Normal or high PO4 → assess Vit D

High PO4 →
- High PTH is 2 → lung cancer, renal cell carcinoma, pheochromocytoma

Low PO4

- Drugs → lithium
- Familial hypocalcemic hypercalcemia
- Primary hyperparathyroidism → adenoma, hyperplasia, carcinoma
- Tertiary hyperparathyroidism → increased PTH after prolonged secondary hyperparathyroidism due to renal failure

Normal/Low Vit D

High calcitriol

- Excessive intake of vitamin D

- Granulomatous disease (lymphoma, TB, sarcoidosis, Calcitriol intake

High calcitriol

HYPERCALCEMIA

SYMPTOMS
- “Bones, stones, groans and psychiatric overtones”
- MSK → weakness, bone pain
- Renal → nephrolithiasis, polyuria, polydipsia
- Groans → abdominal pain, vomiting, nausea, constipation, pancreatitis
- Psychiatric → psychosis, anxiety, depression Neurologic → Hypotonia, hyporeflexia, myopathy, paresis

MANAGEMENT
- IV NS +/- furosemide to increase renal excretion
- Calcitonin – onset in hours but develop tachyphylaxis
- Bisphosphonates – onset 1-2 days, inhibits osteoclasts
- Glucocorticoids – if malignancy, vitamin D intoxication, granulomatous disease
- Denosumab – for malignancy related
- Hemodialysis – if resistant to other treatment
Acute Kidney Injury

Pre-Renal
- Decreased effective circulatory volume
  - Hypovolemia
  - CHF
  - Sepsis
- Renal vasoconstriction
  - NSAIDs
  - ACEI/ARB
  - Contrast
- Large vessel
  - Renal artery stenosis
  - Vasculitis
  - Dissection
  - VTE

Post-Renal
- Bladder neck
- Ureteral – bilateral
  - BPH
  - Prostate cancer
  - Neurogenic bladder
  - Anticholinergic
- Malignancy
  - Lymphadenopathy
  - Nephrolithiasis

Renal
- Acute Interstitial Nephritis
  - Allergic (B-lactam, NSAIDs, PPI)
  - Infection (pyelonephritis, legionella, TB)
  - Infiltrative (sarcoid, lymphoma, leukemia)
  - Autoimmune (Sjogren’s, SLE)
- Acute Tubular Necrosis
  - Ischemia (progression of pre-renal)
  - Toxins (drugs, pigments, antibodies)
  - Contrast
- Glomerulonephritis
  - Cholesterol emboli
  - Hemolytic uremic syndrome
  - DIC
  - Malignant HTN
- Small-medium Vessel
ACUTE KIDNEY INJURY

DEFINITION
- AKI: Abrupt (<48h) increase in Cr ≥ 50% or ≥27 µmol/L or urine output < 0.5mL/kg/h for ≥ 6h
- Note: Cannot estimate GFR using Cr in the setting of AKI because not in steady state

SYMPTOMS
- Fatigue, oral intake, nausea/vomiting/diarrhea
- Recent procedures and changes to medications
- Past medical history of vascular or systemic disease
- Recent infection
- Dysuria, nocturia, frequency, incomplete emptying

SIGNS
- Volume status – volume overload in CHF vs. hypovolemia
- Signs of obstruction, vasculitis, or systemic disease

INVESTIGATIONS – OLIGURIA OR ANURIA

GENERAL
- CBC, electrolytes + Ca²⁺, PO₄³⁻, Cr, urea
- Renal Ultrasound or CT
  - rule out obstruction and evaluate kidney size
  - hydronephrosis suggests post-renal cause
- Renal biopsy if etiology is unclear

URINE EVALUATION - MICRSCOPY AND ELECTROLYTES

Pre-renal
- Bland, transparent hyaline casts
- FE₉Na<1%, BUN:Cr >20, U₉Na < 20, Uₒsm>500

Renal
- Acute tubular necrosis
  - Pigmented granular muddy brown casts, RBCs and protein from tubular damage
  - FE₉Na>2%, BUN:Cr <20, U₉Na > 20, Uₒsm<350
- Acute interstitial nephritis
  - WBCs, WBC casts, +/-RBCs with negative urine culture
  - Urine eosinophils in abx
  - Lymphocytes in NSAIDs
- Small-med vessel disease
  - RBCs +/- urine eosinophils in cholesterol emboli
- Glomerulonephritis
  - RBC casts, Dysmorphic RBCs

Post-renal
- Post-residual volume > 200mL suggests obstruction
- Bland urinalysis +/- non-dysmorphic RBCs
- FE₉Na variable

MANAGEMENT

PRE-RENAL
- Fluid resuscitation
- Avoid nephrotoxins, Hold ACEI/ARB and NSAIDs
- Dialysis (see indications below)

RENA
- Address reversible renal causes: discontinue nephrotoxic drugs, treat infections and optimize electrolytes
- Correct ECF volume, supportive care, consider corticosteroids and immunosuppressive therapy
- Avoid contrast dye
- Dialysis (see indications below)

**POST-RENAL**
- Foley catheter for post-renal obstruction
- Treatment for BPH (ex. Tamsulosin, TURP)
- Dialysis (see indications below)

**INDICATIONS FOR DIALYSIS (AEIOU)**
- A – Refractory acidemia
- E – Electrolyte disorder, most importantly hyperkalemia
- I – Intoxications (methanol, ethylene glycol, metformin, salicylates, lithium, valproic acid, barbiturates, theophylline, thallium)
- O – Overload of volume
- U – Uremia (pericarditis, encephalopathy, bleeding)
Chronic Kidney Disease

CHRONIC KIDNEY DISEASE

DEFINITION
- ≥3 months of reduced GFR (<60) and/or kidney damage based on pathology, markers, or imaging

ETIOLOGY
- Diabetes (45% of CKD)
- Hypertension/RAS (27% of CKD)
- Glomerular disease
- Interstitial disease
- Polycystic kidney disease/Congenital
- Drugs
- Multiple Myeloma
- Progression of AKI

STAGING

<table>
<thead>
<tr>
<th>Stage</th>
<th>GFR mL/min/1.7 m²</th>
<th>Goals of Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (normal)</td>
<td>&gt;90</td>
<td>Diagnosis and treatment of underlying condition and comorbidities</td>
</tr>
<tr>
<td>2 (mild)</td>
<td>60-89</td>
<td>Estimate progression</td>
</tr>
<tr>
<td>3a (mild-moderate)</td>
<td>45-59</td>
<td>Evaluate and treat complications</td>
</tr>
<tr>
<td>3b (moderate-severe)</td>
<td>30-44</td>
<td>Evaluate and treat complications</td>
</tr>
<tr>
<td>4 (severe)</td>
<td>15-29</td>
<td>Prepare for renal replacement therapy</td>
</tr>
<tr>
<td>5 (kidney failure)</td>
<td>&lt;15</td>
<td>Dialysis if uremic</td>
</tr>
</tbody>
</table>

SIGNS AND SYMPTOMS – UREMIA
- General - Fatigue, generalized weakness, anorexia, nausea, decreased temperature
- Neurologic - Encephalopathy (decreased memory and attention), myoclonic jerks, seizures, altered smell and metallic taste, restless leg syndrome, impaired sleep, neuropathy
- Cardiovascular – Pericarditis, accelerated atherosclerosis, hypertension, volume overload
- Hematologic – Anemia, bleeding (platelet dysfunction and EPO deficiency)
- Metabolic – hyperkalemia, hyperphosphatemia, acidosis, hypocalcemia, secondary hyperparathyroidism, osteodystrophy
- Dermatologic – pruritus, uremic frost, sallow, calciphylaxis

INVESTIGATIONS
- CBC, electrolytes, urea, creatinine
- Glucose, HbA1C – diabetes
- Ca, PO4, Mg, PTH – electrolyte imbalance
- Fasting lipid profile
- Urinalysis, 24h urinary albumin, 24h urinary protein collection
- Myeloma work up (serum protein electrophoresis, urinary protein electrophoresis)

MANAGEMENT

GENERAL
- Nephrology referral when GFR <30
- Access planning
- Vaccines (flu, pneumovax, HBV)
- Avoid nephrotoxins and unknown OTCs or herbals
- Diet: low Na, K and PO4
### MANAGE CARDIOVASCULAR RISK FACTORS

- Blood pressure control with Angiotensin Converting Enzyme (ACE) inhibitor (ramipril) or Angiotensin II Receptor Blocker (ARB), monitor creatinine and K in 1-2 weeks and discontinue if Creatinine increases by >30% or K >5.4
  - ACEis inhibits Angiotensin Converting Enzyme which converts Angiotensin I to Angiotensin II
  - ARBs block angiotensin II AT₁ receptors
  - Lead to vasodilation of efferent arterioles -> decreases intraglomerular pressure -> decreases long term remodeling and stress on the kidney -> slow progression of CKD
  - Decrease blood pressure
  - Decrease proteinuria
  - Decrease mediators of glomerular tubule hypertrophy and fibrosis

- Lipid control
- Smoking cessation
- Diabetes control/treatment

### TREAT COMPLICATIONS

- Acidosis - Sodium bicarbonate or sodium citrate if low HCO₃⁻
- Electrolyte imbalance
  - Hyperkalemia – low potassium diet, diuretic, caution with ACE inhibitor
- Overload of volume – diuresis
- Anemia – erythropoietin, target 100 g/L, ensure iron stores replete
- Uremic bleeding – dDAVP if bleeding
- Renal osteodystrophy/ Secondary hyperparathyroidism –
  - If PO4 high and Ca low > calcium carbonate
  - If PO4 high and Ca high > Non-Ca binders (Sevelamer)
  - If PTH above goal then start vitamin D, then add Cacitriol
  - If PTH high despite phosphate binders and calcitriol, then add trial cinacalcet or consider parathyroidectomy

### References

Neurology
Approach Mononeuropathy and Polyneuropathy

- Carpal tunnel syndrome (median nerve)
- Foot drop (peroneal nerve)

Mononeuropathy

- Vasculitis (PAN, Churg-Strauss, Wegner’s, cryo, SLE, RA, Sjogren’s)
- T2DM
- Lyme
- Leprosy
- HIV
- Amyloid
- Sarcoidosis
- Lymphoma

Mononeuropathy Multiplex

- DM
- EtOH
- Vit B12 def
- Paraneoplastic
- Amyloid
- Chemotherapy
- Heavy metals
- Porphyria
- AIDP/GBS, CIDP
- Hypothyroidism
- Uremia
- Sepsis
- HIV
- Lead

Polyneuropathy
# Peripheral Neuropathy

## Definitions
- Peripheral neuropathies affect the peripheral nerve anywhere from the plexus → NMJ
- Mononeuropathy affects a single nerve and usually due to entrapment, compression or trauma
- Polyneuropathy affects multiple symmetric nerves
- Mononeuropathy multiplex affects multiple noncontiguous nerves

## Symptoms
- Timing: acute vs chronic, relapsing/remitting vs constant vs progressive
- Distal muscle weakness, muscle cramps
- Numbness, paresthesia
  - Burning dysesthesia (small fibre), ataxia (large fibre)
- Autonomic symptoms: dry mouth, diaphoresis, orthostatic hypotension, gastroparesis, bladder/bowel dysfunction

## Signs
- LMN signs: muscle atrophy, fasciculations, hyporeflexia or absent reflexes
- Single peripheral nerve distribution of sensory loss → mononeuropathy
- Glove and stocking distribution of sensory loss → polyneuropathy
- Unusual presentations: Mononeuritis multiplex: involving >2 separate nerve areas, due to vasculitis. Lead poisoning → pure motor deficits. Vitamin B6 toxicity, paraneoplastic syndrome → pure sensory deficits. GBS and CIDP: not true neuropathies, better name = polyradiculoneuropathies.

## Investigations
- Differentiate motor vs sensory vs mixed vs autonomic
- Distal symmetric polyneuropathy: CBC, lytes, Creat, HbA1C, B12, TSH, ESR, SPEP
- Based on H&P: LFTs, ANA, Anti-Ro/La, HIV, Cu, Lyme titers, RPR, UA, UPEP, ANCA, heavy metal screen, LP, cryoglobulins, paraneoplastic panel
- Nerve conduction studies: can differentiate mononeuropathy vs polyneuropathy
- Electromyogram: can differentiate neuropathy vs myopathy
- Nerve biopsy: rarely done, leave patients with deficits, to RO vasculitis in mononeuropathy multiplex

## Management
- Manage/treat underlying cause
  - Carpal tunnel syndrome: splint, surgery
  - Diabetic neuropathy: manage blood glucose
- Manage neuropathic pain
  - 1st line: TCAs, SNRIs, gabapentinoids
  - 2nd line: Tramadol, opioids
  - 3rd line: Cannabinoids
  - 4th line: Methadone, tapentadol, anticonvulsants, topical lidocaine
- Physical therapy
**Stroke**

### STROKE

#### DEFINITIONS

- Sudden interruption of vascular supply to brain ➔ acute neurological deficit
  - Stroke = infarction of CNS tissue, irreversible damage
  - TIA = same symptoms and signs, no imaging evidence of infarction, full recovery
- 2 major types of stroke: ischemic (80% of strokes) and hemorrhagic (20%)

#### PATHOPHYSIOLOGY

- Ischemic strokes from cardioembolic events (ex. Thrombus from the heart in atrial fibrillations), vascular disease (ex. Large vessel disease – atherosclerosis leading to plaques causing stenosis/occlusion vs. small vessel disease – lacunar strokes) or cerebral hypoperfusion
- Hemorrhagic stroke from intracranial hemorrhage (bleed from cerebral arteries secondary to hypertension) or subarachnoid hemorrhage (bleed from major cerebral arteries such as aneurysm rupture)

#### SYMPTOMS

- Onset: time last seen well, usually sudden onset neurological deficit(s)
  - Focal neurological deficits suggest ischemic stroke or ICH
- PMHx: HTN, dyslipidemia, diabetes, smoking, family Hx, cardiovascular disease (carotid stenosis, A.fib), previous stroke or TIA
  - Risk factors specific to hemorrhagic stroke: trauma, illicit drug use (ICH), aneurysm/familial form of aneurysm (SAH)
- Thunderclap headache = SAH due to aneurysmal rupture

#### SIGNS

- Stroke syndromes = specific deficits depending on which region of brain is affected
  - ACA = Frontal lobe
    - Hemiplegia (leg > arm), cognitive deficits, personality change/abulia
  - MCA = Posterior frontal lobe, temporal and parietal lobes
    - Hemiplegia (face and arm > leg) and hemianesthesia
    - Homonymous hemianopia/Ipsilateral gaze preference (due to damage to frontal eye fields)
    - Aphasia if dominant hemisphere affected
    - Neglect if non-dominant hemisphere affected
  - PCA = Occipital lobe
    - Contralateral homonymous hemianopia sparing macula
    - Thalamic involvement ➔ contralateral hemisensory loss
  - Basilar artery = Brainstem
    - Crossed findings: ipsilateral CN deficits, contralateral motor deficits
    - Cerebellar involvement ➔ ataxia, nystagmus, vertigo
    - Depressed respiration, bradycardia, loss of consciousness
  - Cerebellar
    - Vertigo, diplopia, dysarthria, nystagmus, ipsilateral limb ataxia
  - Lacunar arteries = Internal capsule, thalamus
    - 5 major syndromes: pure hemiplegia, pure hemianesthesia, ataxic hemiparesis, dysarthria and clumsy hand, missed sensorimotor
    - No cortical deficits i.e. aphasia, apraxia, visual field deficits
- SAH: signs of irritation of meninges (ex: nuchal rigidity; positive Kernig’s and Brudzinski’s signs)

#### INVESTIGATIONS

**ACUTE**

- STAT CT head without contrast ➔ R/O hemorrhage,
CT angio head and neck if endovascular intervention indicated
  o Ischemic stroke:
    ▪ CBC, INR: platelet and INR are part of contraindications to fibrinolytic therapy
    ▪ ECG: for A.fib, MI
  o Hemorrhagic stroke: hyperdense fluid (blood)
    ▪ LP: if CT negative but suspected SAH
    ▪ CT or MR angiogram: visualize vessel with aneurysm

WORKUP FOR ETIOLOGY AND MODIFIABLE RISK FACTORS
  • Holter to assess for AF
  • Echo to assess for thrombus/vegetation, bubble study if PFO suspected
  • Carotid U/S and Doppler (if no vessel imaging obtained in acute evaluation)
  • Labs: lipids, HbA1C

MANAGEMENT

ACUTE INTERVENTION – ISCHEMIC STROKE
  • Antifibrinolytic therapy = tPA, within 4.5h of onset – CONTRAINDICATIONS: hemorrhagic stroke, prior ICH, head trauma or prior stroke in last 3 mths, intracranial neoplasm or AVM, recent intracranial/intraspinal surgery, active internal bleeding, HTN > 185/110, platelets <100, anticoagulant use and INR >1.7
  • Antiplatelet therapy – ASA 81mg at presentation/if TPA contraindicated
  • BP – lower to <185/110 to consider lysis; if lyse keep <180/105, otherwise permissive hypertension unless >220/120
  • Anticoagulant therapy indicated in the setting of atrial fibrillation – DOACs or warfarin
  • Endovascular thrombectomy: if anterior circulation prox cutoff and within 6h of symptom onset

ACUTE INTERVENTION – HEMORRHAGIC STROKE
  • Stabilize and monitor (ICU) – ECG for arrhythmias
  • Lower BP < 160 : IV labetalol
  • Nimodipine: to reduce vasospasm
  • Hold/reverse anticoagulants if patient is taking them
  • Lower elevated ICP: raise head of bed to 30°
  • Specific management for SAH – Stop source of bleeding: endovascular coiling
  • Specific management for ICH – CT or MR angio to look for vascular malformations (ex: AVM) as cause, address

SECONDARY PREVENTION – ISCHEMIC STROKE
  • Antiplatelet therapy: Aspirin and clopidogrel for 90 days then single antiplatelet therapy
  • Anticoagulation therapy: instead of antiplatelet in atrial fibrillation
  • Screen for and manage: HTN, dyslipidemia, diabetes,
  • Smoking cessation
  • Carotid revascularization indicated for: symptomatic carotid stenosis 70-99%, asymptomatic stenosis 70-90%

References
**Oncology**

**Approach to Lymphadenopathy**

- **Infectious**
  - Viral: HIV, EBV, CMV, HSV, VZV, Hepatitis, measles, rubella
  - Fungal and parasitic: histoplasmosis, coccidioidomycosis, toxoplasmosis
  - Bacterial: Generalized: TB, atypical mycobacterial, syphilis, brucellosis, leptospirosis. Localized: streptococci, staphylococci, cat-scratch, tularemia

- **Immunologic**
  - Collagen vascular disease
  - Drug hypersensitivity
  - Serum sickness
  - Histiocytosis X
  - Castleman’s

- **Neoplastic**
  - Lymphoma
  - Leukemia
  - Metastatic carcinoma

- **Other**
  - Sarcoidosis
  - Amyloidosis
  - Lipid storage disease
## Lymphadenopathy

### Symptoms
- Localized infectious symptoms: URTI, cellulitis
- Constitutional symptoms: malignancies, TB
- Timing: acute vs chronic
- Exposures: cats, ticks, HIV, travel history, sexual history
- Joint pain and swelling, rashes ➔ connective tissue disorder
- Pruritis ➔ Hodgkin lymphoma
- Meds ➔ serum sickness
  - Allopurinol, Captopril, Carbamazepine, Hydralazine, Penicillin, Sulfonamides

### Signs
- Determine localized vs generalized
  - Localized = reactive (Ex: cellulitis) or neoplastic
    - Cervical
    - Right supraclavicular
    - Left supraclavicular
    - Axillary
    - Epitrochlear
    - Inguinal
- Check for splenomegaly

### Investigations
- CBC, blood film
- Localized:
  - No symptoms suggesting malignancy ➔ observe for 3-4wk, if no resolution by then ➔ excisional biopsy
  - US
- Generalized:
  - ANA, ESR
  - LFTs
  - SPEP
  - EBV, CMV, HIV serologies
  - VDRL test
  - TB tests
  - CXR, +/- CT thorax and abdomen
  - Biopsy – excisional if suspected lymphoma
Approach to Weight Loss

Weight Loss

Medical
- Malignancy
- Infectious
- GI (PUD, celiac disease, IBD)
- Endocrine (DM, TSH, adrenal insufficiency)
- Organ failure
- Medications
- B12, folate, iron deficiencies

Psychological
- Depression
- Psychosis
- Grief
- Intentional weight loss
- Alcoholism
- Dementia
- Anorexia nervosa/bulimia

Social
- Poverty
- Isolation
- Neglect
- Abuse
- Caregiver fatigue

Physiological
- Anorexia of aging in elderly

Functional
- Immobility
- Arthritis
- Stroke
- Parkinson’s disease
- Dental problems
- Vision or hearing impairment
- Constipation
WEIGHT LOSS

DEFINITIONS

• Clinically significant weight loss: loss of >5% of body weight over 6-12 months

SYMPTOMS

• Pattern of weight loss: recent, progressive → more concerning
• Screen for eating disorders, intentional weight loss/ dieting, and malnutrition
• Review of systems
• Functional factors: dysphagia, poor dentition, poor cognition
• PMHx: Recent/chronic illness, Medications/substances that can causes anorexia, dry mouth, altered taste/smell, nausea/vomiting , Social Hx: impaired ADLs and IADLs, financial situation, living situation (e.g., living alone)

SIGNs

• Weigh the pt: BMI <23.5 in males and <22 in females is concerning
• Inspection: temporal wasting, muscle wasting, triceps skin fold
• Examine for nutritional deficiencies: Increased bruising → vitamin K deficiency; Glossitis → iron deficiency; Ataxia, loss of vibration sense/proprioneception → B12 deficiency; Edema, muscle atrophy → protein deficiency; Cheilosis, painless glossitis, acrodermatitis, angular stomatitis → vitamin B deficiency
• Cognitive and neurological exam: dementia screen
• Full examination looking for underlying diseases process to explain weight loss

INVESTIGATIONS

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Dx</th>
<th>Investigations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever, fatigue</td>
<td>Infection, autoimmune, malignancy, diabetes, thyroid disease</td>
<td>CBC, ESR, CRP, glucose, TSH, LFTs, urinalysis, age-appropriate cancer screening, CXR, abdominal U/S</td>
</tr>
<tr>
<td>Dysphagia, oral problems</td>
<td>Ill-fitting dentures, dental caries/abscess, periodontal disease, esophageal stricture/webs</td>
<td>Visual exam, swallowing study, endoscopy</td>
</tr>
<tr>
<td>Dyspnea, exertional fatigue</td>
<td>CHF, pulmonary infection, emphysema, COPD</td>
<td>CBC, CXR, ECG, basic metabolic panel</td>
</tr>
<tr>
<td>Indigestion, abdominal pain, change in stool pattern, early satiety</td>
<td>GI malignancy, PUD, dyspepsia, GERD, cholecystitis</td>
<td>CBC, ESR, CRP, FOBT, LFTs (albumin, INR, bilirubin), abdominal U/S, endoscopy, colonoscopy</td>
</tr>
</tbody>
</table>

MANAGEMENT

• Multidisciplinary team: dentists, dieticians, speech/ occupational/ speech therapists, social workers
• Dietary changes: minimize dietary restrictions, eat high-calorie foods, softer food consistency (if chewing/swallowing problem)
• Environmental changes: eat in company or with assistance (hand-feeding pt)
• Nutritional supplements (e.g., Ensure, Glucerna): provide extra calories but should not replace meals
• Flavor enhancers (e.g., bacon, ham flavours): maximize taste and smell
• Appetite stimulants: Megestrol acetate → improves appetite and increases weight gain in patients with cancer
• If depression + weight loss → consider Mirtazapine (NaSSA)
• If idiopathic (i.e., cannot identify underlying cause) → watchful waiting for 1-6 mo (shorter interval if progressive weight loss). On follow-up, consider diet, psychosocial causes, drug use, occult illness
Oncological Emergencies

**HYPERCALCEMIA - SEE APPROACH TO ELECTROLYTES IN NEPHROLOGY**

**BACKGROUND**
- Hypercalcemia of malignancy typically has markedly elevated calcium levels, patients can be very symptomatic (symptoms depend on Ca level as well as rate of rise)
- Hypercalcemia associated with malignancy thought to be caused by a variety of mechanisms:
  - PTH-related protein (PTHrP) produced by tumour cells
  - Ectopic PTH production
  - Metastasis to bone
  - Osteolytic metastases (Ex: Multiple Myeloma)
  - Ectopic 1,25-dihydroxycholecalciferol production (Ex: Lymphoma)

**SUPERIOR VENA CAVA SYNDROME**

**BACKGROUND**
- SVC compression by a malignant mass (ex: small cell & non-small cell bronchogenic carcinoma, lymphoma, metastases) or non-malignant cause (Ex: goiter, upper limb DVT)

**SYMPTOMS**
- Edema of face or arms (80%)
- Dyspnea or cough
- Dysphagia – from external compression of esophagus
- Headache
- Dizziness

**SIGNS**
- Venous distention in chest and neck
- Stridor – from external compression of airway
- Pemberton’s sign – facial flushing with upper limb elevation
  - Increased venous return to SVC, obstruction forces blood to collateral veins → flushing

**INVESTIGATIONS AND MANAGEMENT**
- Contrast enhanced CT
- ABCs, supportive care – O2, elevate head of bed
- High dose steroids (dexamethasone) and diuretic to decrease inflammation and edema
- Urgent chemotherapy/radiation to decrease mass size
- Stenting of SVC
- Systemic anticoagulation if thrombus is present

**CEREBRAL METASTASIS**

**BACKGROUND**
- Most common intra-cranial tumour (more common than primary brain tumours)
- Most common sources are lung (44%), breast (10%), renal (7%), GI (6%) and melanoma (3%)
- Most common mechanism of spread is hematogenous

**SYMPTOMS**
- Vary depending on which area of brain is affected
- General symptoms – Headache, N/V, seizure, problems with memory, aphasia, can present with focal neurologic deficit

**SIGNS**
- Vary depending on which area of brain is affected but can include
  - Weakness or numbness in legs/arms/face
  - Ataxia
### Confusion
- Signs of increased intracranial pressure—Papilledema, altered LOC

### INVESTIGATIONS AND MANAGEMENT
- Metastatic workup to identify primary tumour
- CT head with contrast—multiple round, well-circumscribed, ring enhancing lesions with surrounding edema. *MRI is more sensitive than CT.*
- High dose dexamethasone to reduce edema
- Consider chemotherapy or radiation therapy based on size and number of lesions
- Surgical approach for single solitary lesions followed with radiation
- Anticonvulsant prophylaxis if presented with seizures

### SPINAL CORD COMPRESSION

#### BACKGROUND
- Metastasis to vertebral column extend causing spinal cord compression
  - Most common area = thoracic spine
- Can be caused by any cancer, but most common are prostate, breast and lung cancer
- Emergency because early Dx/Tx can preserve neurological function

#### SYMPTOMS
- Spinal pain—band-like, neuropathic features, worse when lying down
- Numbness in affected dermatomes

#### SIGNS
- Weakness in affected myotomes and sensory loss in affected dermatomes
- Autonomic dysfunction—Urinary retention, bowel incontinence
- Spinal cord reflexes—loss of anal wink and sphincter tone
- UMN signs—hyperreflexia, upgoing plantar reflex (Babinski)

#### INVESTIGATIONS AND MANAGEMENT
- Urgent whole spine MRI should be done in any cancer patient with acute and severe back pain
  - *Do NOT wait for neurologic signs to develop as this worsens patient recovery and outcome*
- Dexamethasone 10mg IV stat, then 4mg IV or PO q6h
  - *Do not wait for imaging to begin steroid*
- Urgent radiation or surgical decompression if compression or neurological deficits confirmed
## Multiple Myeloma

### BACKGROUND
- Hematological cancer, neoplastic proliferation of plasma cells
  - Neoplastic proliferations of plasma cells → leads to production of monoclonal immunoglobulin = M-protein
    - M-protein increases blood viscosity
    - Ig light chain is insoluble → accumulation as amyloid → end-organ damage
  - Monoclonal antibodies decrease osteoblast activity and increase osteoclast activity → bone disease and increased calcium

### SYMPTOMS
**CRAB** = hyperCalcemia, Renal failure, Anemia, Bone pain (not all patients present with CRAB)
- HyperCalcemia – N/V, constipation, diabetes insipidus (polyuria/polydipsia), depression
- Renal failure – decreased urine output
- Anemia (normocytic) – fatigue, weakness
- Bone pain – pathologic fractures or lytic lesions
- Recurrent infections – clonal plasma cell suppression of normal Ig
- Headaches, stroke, angina, MI – from hyperviscosity of the blood and coagulopathy secondary to inhibition of the antibody against clotting factor

### SIGNS
- HyperCalcemia – confusion
- Renal failure – edema
- Anemia – pallor
- Bony tenderness, usually along the vertebral column
- Thrombocytopenia – bleeding, petechiae, purpura
- Weight loss

### INVESTIGATIONS
- CBC – normocytic anemia, leukopenia, thrombocytopenia
- Blood film – Rouleaux formation
- Renal function – elevated Cr and BUN
- ACR/PCR or 24h urine collection – proteinuria
- Serum protein electrophoresis – elevated M-protein
- Urine protein electrophoresis – Bence-Jones protein + (= light chains in urine)
- Serum free light chain assay
- Bone marrow aspirate and biopsy – >10% plasma cells, abnormal morphology
- Skeletal survey (plain radiographs) – Osteolytic lesions or areas at risk for pathological fractures

### MANAGEMENT
- No curative treatment
- Autologous stem cell transplant can increase survival if indicated – generally if age <65
- Chemotherapy can increase survival in patients not eligible for transplant or as induction prior to transplant
- Proteasome inhibitors (Bortezomib), immunomodulators (Lenalidomide) and immunotherapy also considered for induction; Other active drugs include prednisone, dexamethasone and melphalan
- Supportive management
  - Bone – bisphosphonates for lytic lesions and hypercalcemia, radiation for symptomatic lesions
  - Renal – avoid nephrotoxic medications and consider plasmapheresis for AKI
  - Hyperviscosity – plasmapheresis
  - Recurrent infections – IVig
### ADDITIONAL INFORMATION

#### MM DIAGNOSTIC CRITERIA
- Clonal bone marrow plasma cells ≥ 10% or biopsy proven plasmacytoma and ≥1 myeloma-defining event
  - Myeloma-related end organ or tissue impairment
    - Lytic bone lesion, Ca > 2.75 mmol/L, Cr>176.8 umol/L or Hb < 100 g/L
  - Any of the following biomarkers
    - Bone marrow plasma cells ≥ 60%, serum free light chains ratio ≥ 100:1, >1 focal lesion on MRI studies

#### MONOCLONAL GAMMOPATHY OF UNCERTAIN SIGNIFICANCE
- M protein <3 g/dL, marrow plasmacytosis <10%, no myeloma defining event nor amyloidosis
- Prognosis: 1%/year or 25% lifetime risk of progression to MM, WM, amyloidosis or lymphoproliferative disease

#### SMOLDERING MM
- M protein >3 g/dL or plasmacytosis >10%, no myeloma defining event or amyloidosis
- Prognosis: 10%/year risk of progression

#### WALDENSTROM’S MACROGLOBULINEMIA
- B-cellneoplasm (lymphoplasmacytic lymphoma) that secretes monoclonal IgM
- Clinical manifestations: Anemia, hepatomegaly/splenomegaly/lymphadenopathy (Tumor infiltration), hyperviscosity syndrome, type 1 cryoglobulinemia, amyloidosis/glomerulopathy (IgM deposition), AIHA, Peripheral neuropathy
### Pain Management

#### Pain

**Background**
- Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage.
- All individuals experience pain differently based on physical, emotional, psychosocial and spiritual aspects.

**Definitions**
- Nociceptive pain – activation of the peripheral nociceptors
- Neuropathic pain – disturbance in the central or peripheral nervous system
- Cancer pain – disease progression, neuropathic pain, bone pain, breakthrough pain, delirium, substance use, depression/anxiety
- Acute pain – less than 6 weeks
- Chronic pain – greater than 3 months, pain persists beyond normal tissue healing, impacts functioning

**Symptoms**
- Edmonton Symptom Assessment System in cancer pain to rate intensity of symptoms from 0 to 10
- Nociceptive pain – somatic: dull and localized pain vs. visceral: crampy pain not well localized
- Neuropathic pain – Burning, shooting, radiating pain localized to dermatomal region

**Management**
- Non-pharmacological management – physiotherapy, acupuncture, massage, family therapy, education, psychotherapy/cognitive behavioural therapy
- Medical management – WHO pain ladder
  - Mild pain: non-opioid (acetaminophen and/or NSAID)
  - Moderate pain: Weak opioids for mild to moderate pain (tramadol, codeine/oxycodone, low dose morphine/hydromorphone)
  - Severe pain: Strong opioids for moderate to severe pain (morphine/hydromorphone)
- Surgical management – celiac plexus block, subarachnoid block, cordotomy, epidural/intrathecal infusion
- Adjuvant therapies
  - Initiate bowel protocol when treating with opioids to prevent constipation
  - TCAs (nortriptyline) – for neuropathic pain
  - Anticonvulsants (gabapentin, pregabalin) – for neuropathic pain
  - Antineoplastic treatments – chemo, radiation, hormonal agents
  - Bisphosphonates – bone metastasis, hypercalcemia
  - Corticosteroids – spinal cord compression, visceral distension, increased ICP

**Pharmacology**
- Acetaminophen
  - Mechanism – COX-2 inhibition
  - Side effects – liver toxicity in elevated doses
- NSAIDs
  - Mechanism – non-selective COX-1 and 2 inhibition reduces pro-inflammatory prostaglandin synthesis
  - Side effects – gastric ulceration/bleeding, decreased renal perfusion, photosensitivity, teratogen
- Opioids
  - Mechanism – decreases nociceptive transmission between 1st and 2nd order neurons in the dorsal horn, activates ascending modulatory pathways resulting in release of inhibitory neurotransmitters, inhibits peripheral inflammatory response and hyperalgesia, affects mood and anxiety
  - Side effects – respiratory depression, constipation and abdominal pain, sedation, nausea and vomiting, pruritus, confusion, dependence.
Nausea Management

NAUSEA

BACKGROUND

- Pathways involved in nausea and vomiting include the chemoreceptor trigger zone in the medulla, vagus nerve stimulation in the GI tract and nociceptive stimuli
- Nausea can be neurologic, gastrointestinal, metabolic, medication or functional

MANAGEMENT

- Non-pharmacological – frequent and small meals, avoid offensive odors, treat constipation
- Pharmacological
  - H1 antagonists – dimenhydrinate, diphenhydramine
  - D2 antagonists – metoclopramide, prochlorperazine, chlorpromazine, haloperidol
  - 5HT3 antagonists – ondansetron
  - M1 antagonists – scopolamine
  - Steroid – dexamethasone
- Treat underlying cause
  - Vestibular disease/vertigo – dimenhydrinate, diphenhydramine
  - Drug induced, hepatic or renal failure – prochlorperazine, haloperidol
  - Gastric stasis – metoclopramide
  - Bowel obstruction – metoclopramide, dexamethasone, octreotide
  - Raised ICP – dexamethasone

References

**Pharmacology**

**Desensitization Therapy**

**BACKGROUND**

- Desensitization alters the immune response to a drug allowing for temporary tolerance of a medication. Through this process patients with drug hypersensitivity reactions can receive an uninterrupted course of the medication.
- Desensitization is accomplished by administering small amounts of the drug and increasing the dose by small increments until the full therapeutic dose is reached.
- This should be done in a monitored setting to observe for any hypersensitivity reaction.

**INDICATIONS**

- Individuals with non-IgE mediated immediate drug reaction (reactions that develop during the infusion or 6 hours after) where no other medication is acceptable.

---

### Pre-operative Medication Management

#### ANTIBIOTICS

- Antibiotics for bacterial prophylaxis is only given to patients with high risk of endocarditis - *amoxicillin 2g PO/IM/IV or cefazolin 1g IV/IM*
  - Prosthetic cardiac valves, cyanotic congenital heart disease, cardiac transplant patients, prosthetic devices
  - Procedures involving the oral cavity, respiratory tract, GI/GU tract if active infection, MSK

#### STEROIDS

- For patients on regular steroids (prednisone >20mg/day for > 3 wks, stress dosing may be required)
  - Minor stress (local anesthetic) – no stress dose
  - Moderate stress (orthopedic, perivascular) – 50mg hydrocortisone IV before OR
  - Major stress (intra-abdominal, cardiac) – 100mg hydrocortisone IV before OR

#### ANTICOAGULATION

- Management based on risk of thrombosis and risk of bleeding with procedure
  - Warfarin – if high risk of bleed, hold warfarin 5 days pre-op and resume 12-24 hours post-op, if emergency surgery can administer vitamin K/FFP/prothrombin complex concentrate
  - Novel oral anticoagulants – discontinue 2-4 days before surgery
  - Bridging with anticoagulation is generally not required unless high risk of thrombosis or prolonged period of discontinuation

#### INSULIN

- Reduce insulin dose by half the night before surgery and hold morning insulin the day of surgery

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### Corticosteroids

#### INDICATIONS

- Replacement – adrenal insufficiency, congenital adrenal hyperplasia
- Acute systemic treatment – anaphylaxis, cerebral edema, exacerbation of asthma, COPD, autoimmune disease, antiemetic in chemotherapy
- Chronic systemic treatment – chronic inflammatory disease (asthma, COPD, IBD), autoimmune disease (sarcoidosis, SLE), steroid responsive dermatoses
- Prophylactic treatment – following organ transplant, prior to preterm delivery

#### SIDE EFFECTS

- MSK – osteoporosis, myopathy, osteonecrosis
• Endocrine – hyperglycemia, cushingoid features, adrenal insufficiency/crisis
• Cardiovascular – fluid retention, edema, weight gain, hypertension, arrhythmias
• Gastrointestinal – gastritis, gastric ulcer formation, GI bleed, pancreatitis, fatty liver disease
• Dermatological – ecchymosis, skin thinning, skin atrophy, acne, hirsutism, facial erythema, stria, impaired wound healing, hair thinning, perioral dermatitis
• Ophthalmological – cataracts, glaucoma
• Psychiatric – depression, psychosis, anxiety
• Infections

References
## Respirology

### Pulmonary Function Tests

### PULMONARY FUNCTION TEST

#### DEFINITIONS

- **PFT** – test performed by patient performing max inspiration, explosive start, smooth 6+ second exhalation, plateau max effort, 3 acceptable curves are required, interpretation of results based on age, height, weight, ethnicity
- **FEV1** – volume expired in one second
- **FVC** – total expired volume
- **TLC** – total lung capacity
- **Vmax, FEF, MMEF** – instantaneous flows during expiration
- **Flow-volume loop** – instantaneous flow versus expired volume

#### INTERPRETATION

- PFT interpreted based on the shape of the loop, FEV1, FVC, and FEV1/FVC
- **Obstructive lung disease**
  - Etiology – asthma, COPD, CF, bronchiolitis
  - Shape of the loop – scooped loop
  - Decreased FEV1/FVC < 0.75
  - FEV1 decreased - >70% = mild, 50% - 70% = moderate, <50% = severe
  - If FEV1 improves 12% or 200mL with SABA this is consistent with reversible airways disease (asthma)
  - If FEV1 does not improve 12% or 200mL this is consistent with irreversible airway obstruction (COPD)
- **Restrictive lung disease**
  - Etiology – IPF, pleural disease, neuromuscular disease, chest wall disease
  - Shape of the loop – tall, peaked and narrow loop
  - FEV1/FVC is normal, FVC is low, TLC is low
  - FVC > 70% = mild, FVC 50% - 70% = moderate, FVC <50% = severe
## Chest X-Ray Interpretation

### CHEST X-RAY INTERPRETATION

#### VIEWS
- Posterioranterior and lateral – patients that can walk and stand
- Anteriorposterior – reserved for bedridden patients
- Decubitus – look for pleural fluid
- Expiratory view – look for pneumothorax

### APPROACH TO READING CXR
- Most important thing is to have a systematic approach, below is an approach going from inside out
- Compare to previous films
- Evaluate patient’s position (AP, PA, upright, supine)
- Assess quality of the film:
  - Inspiration: 5-6 anterior ribs
  - Rotation: clavicles equidistant to spinous process:
- Penetration: vertebral body visible behind heart
- Lungs (compare sides)
- Hemidiaphragms – sharp
- Ribs, clavicle, shoulders, spine
- Soft tissue
- Look under the hemidiaphragms

### COMMON ABNORMALITIES

#### MEDIASTINUM AND HILA
- Wide mediastinum – mediastinal mass, vascular abnormality (aneurysm, dissection)
- Hilar enlargement – adenopathy, dilated pulmonary arteries
- Enlargement of cardiac silhouette – cardiomegaly

#### LUNGS
- Too white – opacification
  - Airspace consolidation (airspaces filled with water, pus, blood or cells) – obscured vessels, air bronchogram, silhouette sign (obscure adjacent structures)
  - Atelectasis – loss of volume leading to displacement of the fissures leading to elevated hemidiaphragm, mediastinal/trachea shift to the abnormal side, ribs closer together on the affected side
  - Interstitial disease – disease of the pulmonary interstitium seen has too many lines (reticular), too many dots (nodular) or too many lines and dots (reticularnodular pattern)
  - Nodule or mass – focal opacity <3cm (nodule) or >3cm (mass)
  - Pleural effusion – fluid in the pleural space such that fluid displaces the lung seen on x-ray as a concave border (meniscus sign)
- Too black – lucent/hyperlucent
  - Pneumothorax – increased air outside of the lung seen by pleural line with no vessels beyond the pleura
  - Emphysema

#### BONES AND SOFT TISSUE
- Fracture
- Soft tissue mass
- Bone destruction
Approach to Hypoxemia

Hypoxemia

Increased A-a gradient

- Administer 100% O₂

  - PₐO₂ improves V/Q mismatch
  - Obstructive lung disease (COPD, asthma)
  - Pulmonary vascular disease (PE)
  - Interstitial lung disease

  - Anatomic (intracardiac shunt, AVMs)
  - Physiologic (atelectasis, pneumonia, ARDS)

Normal A-a gradient

- Increased PₐCO₂ Hypoventilation

  - CNS depression
  - Obesity hypoventilation syndrome
  - ALS (impaired neural conductions)
  - Myasthenia gravis (muscular weakness)

- Normal PₐCO₂

  - Low PₐO₂ (high altitude)
**HYPOXEMIA**

**DEFINITIONS**

- Alveolar to arterial (A-a) oxygen gradient: $P_{A\text{O}_2} - (P_{a\text{O}_2})$, difference between amount of oxygen in alveoli ($P_{A\text{O}_2}$) and amount of oxygen dissolved in plasma ($P_{a\text{O}_2}$)
- $P_{A\text{O}_2} = (\text{FiO}_2 \times (P_{\text{atm}} - P_{H_2O})) - (P_{a\text{CO}_2}/\text{RespQ})$
- $P_{A\text{O}_2}$: partial pressure of alveolar oxygen, $\text{FiO}_2$: fraction of inspired oxygen ($0.21$), $P_{\text{atm}}$: atmospheric pressure ($760\text{mmHg}$), $P_{H_2O}$: H2O pressure in the alveolus ($47\text{mmHg}$), $P_{a\text{CO}_2}$: from the ABG, RespQ: respiratory quotient ($0.8$)

**MANAGEMENT**

- Reverse underlying pathology
- **Oxygen Therapy**: to maintain oxygenation above $P_{\text{aO}_2} \geq 60\text{ mmHg}$ (in most cases)
  - Low-flow (e.g., nasal cannula, simple mask, reservoir mask) vs high-flow (e.g., venturi masks) systems depends on clinical circumstances
  - Improves hypoxemia in hypoventilation, V/Q mismatch, diffusion impairment and low $P_{\text{aO}_2}$
  - Minimal impact on hypoxemia in shunt
- **Ventilation, BiPAP, and PEEP/CPAP**: for more severe hypoxemia; to recruit alveoli and redistribute lung fluid
  - Improves hypoxemia in hypoventilation, intrapulmonary shunt (except one-sided) and V/Q mismatch
  - Worsens hypoxemia in right to left shunt
  - Minimal impact on hypoxemia in low FiO$_2$
  - Intubation may be required if no improvement in $P_{\text{aO}_2}$ with these methods
- **Improve Cardiac Output**: +/- hemodynamic support (fluids, vasopressors, inotropes), reduce $O_2$ requirements
  - Improves hypoxemia in intrapulmonary shunt and V/Q mismatch
  - Worsens hypoxemia in right to left shunt
  - Minimal impact on hypoxemia in hypoventilation and low FiO$_2$
Approach to Chronic Cough

Cough

- Airway Irritants
  - Smoking
  - Foreign body

- Pulmonary
  - CHF
  - GERD
  - Post-nasal drip

- Non-pulmonary
  - ACE inhibitor
  - B-blocker

- Medications

- Airway Disease
  - Asthma
  - COPD
  - Chronic bronchitis
  - Neoplasm
  - External compression by node or mass

- Parenchymal Disease
  - Interstitial lung disease
  - Lung abscess
  - Pneumonia
# CHRONIC COUGH

## DEFINITIONS
- Chronic cough: cough of 8 weeks duration

## SYMPTOMS
- Cough lasting at least 3 months
- Lifestyle and medications → smoking or smoke exposure, recent travel, use of ACEi
- Pulmonary causes → dyspnea, hemoptysis, wheezing, chest pain/tightness, sputum production
- Non-pulmonary causes → rhinitis, symptoms of reflux, post-nasal drip, orthopnea, PND
- Constitutional symptoms → fever, chills, weight loss, night sweats, decreased appetite

## SIGNS
- Conduct complete respiratory exam, HEENT and cardiovascular exam which may show findings of underlying etiology of chronic cough – findings discussed in details in handbook sections covering the specific etiology

## INVESTIGATIONS
- Investigations should be guided by findings on history and physical exam
- If unknown etiology following history and physical exam proceed to investigation flow chart modified from the AAFP 2011 Guidelines – Evaluation of patient with Chronic cough

![Investigation Flow Chart](chart.png)

## MANAGEMENT
- Lifestyle Modifications – Smoking cessation, discontinue medications causing cough
- Treat underlying etiology – Asthma → education, avoid triggers, SABA prn, ICS, GERD → weight loss, diet modifications, PPI therapy, Post-nasal drip → intranasal glucocorticoids
Approach to Pleural Effusion

Pleural Effusion

Transudate
- CHF
- Cirrhosis
- Nephrotic syndrome
- Constrictive pericarditis
- Other: PE, malignancy, myxedema

Exudate
- Lung parenchymal infection/Parapneumonic
- Malignancy
- Pulmonary embolism
- Collagen vascular disease – RA, SLE, Wegener’s
- GI disease – pancreatitis, esophageal rupture, abdominal abscess
- Hemothorax – trauma, PE, malignancy
- Chylothorax
- Other: Asbestos exposure, drug-induced, uremia, post-radiation, sarcoidosis, meigs’ syndrome, yellow-nail syndrome
PLEURAL EFFUSION

DEFINITIONS

- Pleural effusion: excess amount of fluid in the pleural space

INVESTIGATIONS

- Diagnostic Thoracentesis – all effusions > 1cm on CXR in lateral decubitus
  - Pleural Fluid Analysis
    - Protein, LDH
    - pH – empyema <7.2, TB and mesothelioma <7.3
    - Gram stain and culture – infection
    - Cell count differential – check for increased WBC
    - Cytology – malignancy or infection
    - Glucose - <3.3 mmol/L suggests malignancy, infection or RA
    - Rheumatoid factor, ANA – collagen vascular disease
    - Triglycerides - chylothorax
  - Light’s Criteria – criteria for Exudative Effusion
    - Fluid/serum total protein ratio > 0.5
    - Fluid/serum LDH ratio >0.6
    - Fluid LDH > 2/3 upper limit of normal serum level
- CXR or CT chest
  - Determines size of pleural effusion and may show findings of underlying lung pathology
- Bloodwork
  - CBC, lytes, urea, Cr, LDH, total protein, AST, ALT, ALP, bilirubin, INR, PTT, albumin

MANAGEMENT

- Treat the underlying cause
- Thoracentesis for symptomatic relief
- Complicated parapneumonic effusions and empyemas require drainage to achieve resolution
- Pleural catheter or pleurodesis if recurrent

PARAPNEUMONIC EFFUSION

<table>
<thead>
<tr>
<th>Pleural Fluid Analysis</th>
<th>Uncomplicated</th>
<th>Complicated</th>
<th>Empyema</th>
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<tbody>
<tr>
<td>Appearance</td>
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<td>Purulent</td>
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<tr>
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<td>&lt;7.2</td>
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<tr>
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<td>25–100</td>
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</tr>
<tr>
<td>Pus</td>
<td>Absent</td>
<td>Absent</td>
<td>Present</td>
</tr>
</tbody>
</table>
Chronic Obstructive Pulmonary Disease

**COPD**

**DEFINITIONS**
- Progressive airflow limitation caused by airway and parenchymal inflammation
- Usually a mixture of small airways disease (chronic bronchitis) and parenchymal destruction (emphysema)

**PATHOPHYSIOLOGY**
- The main etiology is smoking. Can also be caused by recurrent airway infections, α₁-antitrypsin deficiency.
- Emphysema – “Pink puffer”
  - Dilation and destruction of the lung parenchyma which leads to increased dead space which causes hypercarbia and mild hypoxemia
- Chronic bronchitis – “Blue bloater”
  - Productive cough for 3 or more months in 1 year for greater than 2 years
  - Small airways affected which leads to increased shunting of blood through the lungs causing severe hypoxemia, hypercapnia, pulmonary hypertension and cor-pulmonale

**SYMPTOMS**
- Chronic cough, sputum production, dyspnea
- Exacerbation triggers – infection (tracheobronchitis/pneumonia), CHF, PE, MI – leading to worsening dyspnea, cough, sputum production and increased medication requirements

**SIGNS**
- “Barrel-chest,” accessory muscle use, tripodding on inspection
- Hyperresonance on percussion
- Decreased diaphragmatic excursion
- Decreased breath sounds, increased expiratory phase, ronchi and/or wheezes on auscultation
- Respiratory distress with increased work of breathing in COPD exacerbation

**INVESTIGATIONS**
- Spirometry
  - Obstructive pattern
  - FEV₁/FVC <0.7 without a significant change after bronchodilator use
  - Hyperinflation (increased Residual Volume (RV), increased total lung capacity (TLC), increased RV/TLC)
  - Abnormal gas exchange – low DLCO
- Chest X-Ray – Hyperinflation, flat diaphragms, interstitial markings and bullae
- ABG – Low PₐO₂± high PₐCO₂, low pH
- ECG – Right sided heart strain or RVH – cor pulmonale is a complication of COPD

**MANAGEMENT**

**CLASSIFY THE SEVERITY**

<table>
<thead>
<tr>
<th>Stage</th>
<th>FEV₁</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>≥80%</td>
<td>Mild</td>
</tr>
<tr>
<td>II</td>
<td>50% - 80%</td>
<td>Moderate</td>
</tr>
<tr>
<td>III</td>
<td>30% - 50%</td>
<td>Severe</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;30%</td>
<td>Very severe</td>
</tr>
</tbody>
</table>

**PREVENTATIVE STRATEGIES**
- Smoking Cessation
- Vaccinations (influenza and pneumococcal vaccines)
- Pulmonary Rehabilitation
### TREATMENT OF STABLE COPD

- Stepwise approach to treatment in which move to next step if patient experiences persistent symptoms — LAAC — long acting anticholinergic, LABA — long acting bronchodilator, SABA — short acting bronchodilator, ICS — inhaled corticosteroid
- **Mild COPD** → SABA prn → LAAC or LABA
- **Moderate and severe COPD with infrequent exacerbations** → LAAC or LABA → LAAC + LABA → LAAC + ICS/LABA
- **Moderate and severe COPD with frequent exacerbations** → LAAC + LABA → LAAC + ICS + LABA
  - Home oxygen — prevents cor pulmonale and decreases mortality
    - If PaO2 < 56mmHg OR S, O2 < 89% during rest, exercise or sleep
    - If PaO2 56mmHg – 60mmHg AND presence of pulmonary hypertension, cor pulmonary or erythrocytosis
  - Daily azithromycin can lower the rates of exacerbation but long term benefit is unclear
- *Do not use ICS monotherapy as this can increase pneumonia in COPD patients*

### TREATMENT OF COPD EXACERBATION

- ABC – O2; keep sat >90%
- Bronchodilators
  - Ipratropium (SAAC) → 4-8 puffs q1-2h OR nebulizer 0.5mg q1-2h
  - Salbutamol (SABA) → 4-8 puffs q1-2h OR nebulizer 2.5-5mg q1-2h
- Steroids
  - Prednisolone 30-50mg/d x10-14d PO OR
  - Methylprednisolone 125mg IV q6h x 72h
- Antibiotics
  - Prescribe if two of the following present:
    - Increased sputum purulence
    - Increased dyspnea
    - Increased sputum volume
  - Amoxicillin, doxycycline, levofloxacin, cefuroxime, azithromycin (depending on clinical circumstance; no one drug proven superior to the other)
- Mechanical Ventilation
  - BIPAP – initiate if mod/severe dyspnea, low pH, high P, CO2, RR>25
  - Intubation – consider if PaO2 <55-60, increased P, CO2, decreasing pH and high RR

### PHARMACOLOGY OF COPD MEDICATIONS

- **β2-agonists**
  - Relax airway smooth muscle by stimulating beta2-adrenergic receptors -> increases cAMP and produces functional antagonism to bronchoconstriction
  - Long-acting beta2-agonists (LABA) – formoterol, salmeterol,
  - Short-acting beta2-agonists (SABA) – salbutamol, albuterol
- Antimuscarinic drugs
  - Block the bronchoconstrictor effects of acetylcholine on M3 muscarinic receptors expressed in airway smooth muscle
  - Long-acting antimuscarinic antagonists (LAMAs) – tiotropium, aclidinium, glycopyrronium
  - Short-acting antimuscarinic antagonists (SAMAs) – ipratropium, oxtropium
- Inhaled Corticosteroids
  - Reduces inflammation in the airways
  - ICS combined with LABA more effective than either individually (decrease in mortality)
- Phosphodiesterase-4 (PDE4) Inhibitors
  - Roflumistat reduces moderate and severe
**Asthma**

**ASTHMA**

**DEFINITION**
- Chronic inflammatory disorder characterized by airway hyper-responsiveness and variable airflow obstruction in response to endogenous or exogenous stimuli
- Most common in children and improves in adolescence

**SYMPTOMS**
- Symptoms are chronic with episodic exacerbations of the symptoms
- Wheezing, cough, dyspnea, chest tightness, sputum
- History of “trigger” in asthma exacerbation
  - Respiratory irritants (ex. Smoke, perfume), allergens (ex. pets, dust), infections (ex. URTI, pneumonia), drugs (ex. ASA, NSAIDs, BB), emotional stress, cold air, exercise

**SIGNS**
- Can be normal in the absence of asthma exacerbation
- Wheezing and prolonged expiratory phase
- Presence of nasal polyps, rhinitis, rash if allergic component
- Respiratory distress if asthma exacerbation – increased RR, increased HR, accessory muscle use, diaphoresis, pulsus paradoxus

**INVESTIGATIONS**
- Spirometry – Gold Standard
  - Obstructive pattern (FEV1/FVC < 0.75)
  - FEV1 increased by 12% or 200mL after bronchodilator
- Peak Expiratory Flow (PEF) Variability
  - PEF ≥ 60L/min increase after bronchodilator or ≥20% diurnal variation
- Methacholine challenge
  - FEV1 decreases by 20% with PCO2 < 4mg/mL
- Post-exercise test
  - 10-15% decrease in FEV1 after exercise

**MANAGEMENT**

**GOAL OF TREATMENT**
- Daytime symptoms < 4 times/week
- No nocturnal symptoms < 1 time/week
- No limitation of activity
- Exacerbations mild or infrequent
- No asthma related absence from work
- B2-agonist use < 4 times/week
- PEF or FEV1 > 90% personal best
- PEF diurnal variation < 10-15%

**PREVENTION**
- Education – asthma action plan
- Avoidance of triggers (allergens, irritants)
- Vaccinations (yearly influenza vaccine and pneumococcal vaccine every 5 years)

**CHRONIC ASTHMA**
- Reliever Medications – for quick relief of symptoms
  - Short-acting inhaled B2-agonist (SABA) - salbutamol
**Controller Medications**
- Inhaled corticosteroids (ICS) - budesonide, fluticasone
- Long-acting inhaled β2-agonists (LABA) – salmeterol
- Long-acting antimuscarinics (LAMA) – tiotropium
- Leukotriene receptor antagonist (LTRA) – montelukast
- Theophylline – for hard to control asthma, high side-effect profile
- Anti-IgE therapy – omalizumab

**Initiate medication in a stepwise approach – start at step 1 and step up as needed to gain control**
1. Controller Option (SABA)
2. Add low-dose (ICS); LTRA is second line
3. Add LABA
4. Increase dose of ICS + LABA; +LAMA
5. Oral steroids; anti-IgE therapy

**TREATMENT FOR ASTHMA EXACERBATION**
- **ABC** – O2; keep sat >90%
- **Bronchodilators**
  - Salbutamol (SABA) → 4-8 puffs OR nebulizer 2.5-5mg q20min
  - Ipratropium (SAAC) → 4-6 puffs OR nebulizer 0.5mg q20min if severe exacerbation
- **Steroids**
  - Prednisone 0.5-1 mg/kg po
  - Methylprednisolone 125mg IV q6h if severe exacerbation
- **Magnesium** 2g IV - for severe exacerbation
- **Invasive ventilation**
  - For patients with severe exacerbation, decreased LOC and impending respiratory failure
- **Disposition** – determine after 1-3hr of management
  - Discharge home if PEF≥70% and S\textsubscript{a}O\textsubscript{2}≥90% for 60 min.
  - Consider admit to hospital if PEF 40-60% with mild to moderate symptoms, more likely to admit for there are issues with compliance and risk factors for near-fatal asthma
  - Admit to ICU if PEF <40% P\textsubscript{a}O\textsubscript{2} <60 or P\textsubscript{a}CO\textsubscript{2} ≥42 with severe symptoms
## Obstructive Sleep Apnea

### OSA

#### DEFINITIONS
- Episodic decreases in airflow during sleep
- Pharyngeal collapse → apnea (≥10 s) or hypopnea (decreased airflow) ± desaturation

#### CONSEQUENCES
- Apnea and arousals at night cause SNS activation and negative intrathoracic pressure which can increase preload and afterload which leads to cardiovascular complications

#### SYMPTOMS
- **Epworth Sleepiness Scale** used as a screening questionnaire
- Sleep habits → Habitual Snoring, witnessed apneas/gasping, morning headaches
- Daytime dysfunction → Daytime sleepiness, falling asleep while driving
- Cardiovascular complications → Dyspnea, cough, loss of exercise capacity
- Cognitive complications → Short term memory loss, impaired concentration
- Symptoms related to hypoxemia

#### SIGNS
- Often associated with obesity, increased neck circumference
- Signs are related to the complications of chronic OSA and hypoxemia including
  - HTN which increases risk of stroke, CAD and death
  - Polycythemia
  - Pulmonary HTN
  - CHF/cor pulmonale
  - Nocturnal angina
  - Arrhythmias

#### INVESTIGATIONS
- Overnight Polysomnography (Sleep Test) – Evaluate sleep stages, airflow, ribcage movement, ECG, SaO2, limb movements – diagnosis of sleep apnea when apnea/hypopnea index >5

#### MANAGEMENT
- Lifestyle Changes: weight loss, leep hygiene (avoid day time napping, avoid caffeine, reduce alcohol intake, exercise regularly, maintain regular sleep schedule)
- CPAP

### ADDITIONAL INFORMATION – SCREENING TOOL FOR OSA

STOP-BANG is validated questionnaire to assess if further testing is required

<table>
<thead>
<tr>
<th>Question</th>
<th>Risk Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes to 0-2 questions: Low risk</td>
<td></td>
</tr>
<tr>
<td>Yes to 3-4 questions: Intermediate risk</td>
<td></td>
</tr>
<tr>
<td>Yes to 5-8 questions: high risk</td>
<td></td>
</tr>
</tbody>
</table>

- **S** – Do you **Snore** **Loudly**?
- **T** – Do you often feel **Tired, Fatigued, or Sleepy** during the daytime?
- **O** – Has anyone **Observed you stop breathing** or choking/gasping during your sleep?
- **P** – Do you have **high blood Pressure**
- **B** – **BMI** >35 kg/m²
- **A** – **Age** older than 50
- **N** – **Neck** circumference > 17 inches for males, >16 inches for females
- **G** – **Gender** male
Pneumonia

PNEUMONIA

DEFINITIONS

• **Community acquired** – pneumonia acquired in the community caused by S pneumonia (most common), Mycoplasma, Chlamydia (esp in young and healthy), H influenzae, M Catarrhalis (esp in COPD), Klebsiella, GNR (esp in alcoholics and aspiration), S aureus (esp postinfluenza), Legionella (esp in elderly, smokers, decreased immunity)

• **Hospital acquired** – pneumonia acquired in the hospital or in association with health care (hospitalization or abx within 90d, nursing home, home infusion or dialysis in 30d, home wound care, family member with MDR pathogen – S. aureus, Pseudomonas, Klebsiella, E. Coli, Enterobacter, Acinetobacter

• **Immunosuppressed** – pneumonia in a patient with immunosuppression – CAP pathogens + PCP, fungi, NTM, Nocardia, CMV

• **Aspiration** – chemical pneumonitis due to aspiration of gastric contents which can develop into pneumonia after 24-72h – Streptococcus, S. aureus, anaerobes, Pseudomonas, GNB

SYMPTOMS

• Fever, cough with purulent sputum production, shortness of breath, chest pain

SIGNS

• Vitals: fever, tachycardia, hypoxemia, tachypnea

• Crackles on auscultation

• Signs of sepsis or respiratory distress if severe

INVESTIGATIONS

• CBC→ elevated WBC

• ABG→ low PaO₂ and high PaCO₂ if severe

• Sputum gram stain and culture, NP swab

• Blood cultures if severe

• CXR (PA and lateral)→ consolidation

• Bronchoscopy if immunosuppressed (suspected TB or PJP), critically ill, failing to respond or chronic pneumonia

MANAGEMENT

PREVENTION

• Pneumococcal vaccine for all persons >65 yo

• Hand hygiene and droplet precautions for patients with pneumonia while in hospital

RISK STRATIFICATION

Table adapted from M. Sabatine Pocket Medicine

<table>
<thead>
<tr>
<th>Class</th>
<th>Score</th>
<th>Mortality</th>
<th>Disposition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I &amp; II</td>
<td>≤70</td>
<td>&lt;1%</td>
<td>Outpatient</td>
</tr>
<tr>
<td>III</td>
<td>71-79</td>
<td>3%</td>
<td>Brief inpatient</td>
</tr>
<tr>
<td>IV</td>
<td>91-130</td>
<td>8%</td>
<td>Inpatient</td>
</tr>
<tr>
<td>V</td>
<td>&gt;130</td>
<td>29%</td>
<td>ICU</td>
</tr>
</tbody>
</table>

Criteria

<table>
<thead>
<tr>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
</tr>
<tr>
<td>Comorbidities</td>
</tr>
<tr>
<td>Exam</td>
</tr>
<tr>
<td>Labs</td>
</tr>
</tbody>
</table>
### Criteria for clinical instability based on TOH CAP Algorithm
- T > 37.8, HR > 100, sBP<90mmHg, RR>24, SPO\(_2\) < 90% on room air, altered LOC

### TREATMENT
- **ABCs** – airway support PRN, supplemental O\(_2\) if hypoxia, IV access
- Community-acquired pneumonia – outpatient
  - Azithromycin or doxycycline for 5 – 7 days if stable and afebrile for 48-72h
- Community-acquire pneumonia – inpatient
  - If severely ill → ceftriaxone 1-2g IV q24h and azithromycin 500mg IV q24h
  - If not severely ill and can tolerate po → levofloxacin 750mg po q24h
  - If ≤1 CAP sign of clinical instability and afebrile for 48-72h discontinue therapy on day 5 if not immunocompromised, 7 days if moderately immunocompromised and 10 days if severe immunocompromised or slow clinical course
- Hospital acquired pneumonia
  - IV Ceftriaxone
  - If concerned about pseudomonas > Pip-tazo
  - If concerned about MRSA or resistant GNR > carbapenem + vancomycin
- Aspiration pneumonia
  - Clindamycin, amox-clav OR B-lactam + flagyl
- When possible de-escalate antibiotics based on culture and sensitivities

### COMPLICATIONS
- Consider in patients with failure to improve on initial antibiotics treatment
- Complications
  - Parapneumonic effusion, empyema, abscess
  - Metastatic infection: endocarditis, meningitis, septic arthritis
  - Sepsis and septic shock
References
7. TOH Clinical Pathway for Community-Acquired Pneumonia
Rheumatology
Approach to Arthritis

Monoarthritis

Acute (<6wks)
- Inflammatory
  - Crystal arthropathy (gout, pseudogout)
  - Seronegative
  - Reactive

- Non-inflammatory

- Infectious
  - Bacterial
  - Viral

- Hemorrhagic
  - Trauma
  - Fracture
  - Blood dyscrasias
  - Clotting disorder

Chronic (>6wks)
- Inflammatory
- Non-inflammatory
- Infectious
- Hemorrhagic
  - Lyme disease
  - Tuberculosis
  - Fungal
  - Tumor
Polyarthritis

Acute (<6wks)
- Crystal arthropathy
  - Crystal arthropathy (gout, pseudogout)
  - Seronegative
  - Reactive

Infectious
- Bacterial
  - Viral (Parvovirus, EBV, Hep B/C, alphaviruses)

Chronic (>6wks)
Early inflammatory

Inflammatory
- Seropositive: RA, SLE, Myositis, systemic sclerosis, systemic vasculitis
- Seronegative: psoriatic, reactive, ankylosing spondylitis, enteropathic arthritis
- Other: Still’s, Behcet’s, sarcoidosis

Crystal arthropathy
- Polyarticular gout
- CPPD

Degenerative
- Osteoarthritis
**ARTHRITIS**

**DEFINITIONS**

- Inflammatory arthritis – joint swelling, warmth, redness, pain, and decreased range of motion, prolonged morning stiffness (>30 min), improvement of pain/stiffness with motion/exercise
- Monoarthritis – inflammation involving 1 joint
- Oligoarthritis – inflammation involving 2-4 joints
- Polyarthritis – inflammation involving ≥ 5 joints

**SYMPTOMS**

- Number of joints involved, timing of arthritis
- Inflammatory arthritis → morning stiffness for > 30 min, improvement of pain with motion/exercise
- Non-inflammatory/degenerative → may have history of trauma, pain with motion that is relieved by rest, morning stiffness for < 30 min, joint instability – buckling, locking, evening pain
- Infectious → history of Lyme disease, STI, rheumatic fever
- Associated symptoms > rash, oral ulcers, chest pain, shortness of breath, GI symptoms, back pain, recent viral infection

**SIGNS**

- Inflammatory arthritis → joint swelling, warmth, erythema, tenderness, decreased ROM, pain with active and passive movement
- Non-inflammatory/degenerative → joint line tenderness, decreased ROM, pain with active and passive movement
- Infectious → may be systemically unwell especially if septic arthritis
- *Arthritis can be distinguished from periarticular disease on exam as periarticular disease generally presents with full ROM and pain greater on active ROM compared to passive ROM*

**INVESTIGATIONS**

**SYNOVIAL FLUID ANALYSIS**

- If joint effusion, synovial fluid analysis from joint aspiration is the best diagnostic test
- Contraindications
  - Absolute – open lesion or suspected infection of the overlying skin
  - Relative – bleeding diathesis, thrombocytopenia, prosthetic joint
- Assess culture and gram stain, cell count and crystals

<table>
<thead>
<tr>
<th>Test</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-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</td>
<td>High</td>
<td>High</td>
<td>Low</td>
<td>Low or high if purulent</td>
<td>Variable</td>
</tr>
<tr>
<td>WBC/mm³</td>
<td>&lt;200</td>
<td>&lt;2000</td>
<td>&gt;2000</td>
<td>&gt;50000</td>
<td>Variable</td>
</tr>
<tr>
<td>% PMN</td>
<td>&lt;25%</td>
<td>&lt;25%</td>
<td>&gt;50%</td>
<td>&gt;75%</td>
<td>Variable</td>
</tr>
<tr>
<td>Culture/Gram stain</td>
<td>NEG</td>
<td>NEG</td>
<td>NEG</td>
<td>POS</td>
<td>NEG</td>
</tr>
<tr>
<td>Crystals</td>
<td>NONE</td>
<td>NONE</td>
<td>PRESENT in gout and CPPD</td>
<td>NONE</td>
<td>NONE</td>
</tr>
</tbody>
</table>
Rheumatoid Arthritis

**DEFINITIONS**
- Chronic, symmetric, debilitating and destructive inflammatory polyarthritis characterized by synovial tissue formation in the affected joints
- Pathogenesis involves over-production of TNF, IL-1 and IL-6. Risk stems from combination of genetic and environmental influences. More common in females with peak incidence between 50-70 yo

**CLASSIFICATION CRITERIA FOR RA – ACR/EULAR**

A total score of ≥6 of 10 is needed from the following criteria:

A. Joint involvement
   - 1 large joint = 0
   - 2-10 large joints = 1
   - 1-3 small joints = 2
   - 4-10 small joints = 3
   - >10 joints (at least one small joint) = 5

B. Serology
   - Negative RF AND negative ACPA = 0
   - Low positive RF OR low positive ACPA = 2
   - High positive RF OR high positive ACPA = 3

C. Acute phase reactants
   - Normal CRP AND normal ESR = 0
   - Abnormal CRP OR abnormal ESR = 1

D. Duration of Symptoms
   - < six weeks = 0
   - ≥ six weeks = 1

**SYMPTOMS**
- Insidious onset of pain, swelling and impaired function of joints
- Morning stiffness >1hr
- Constitutional symptoms – low-grade fever, weight loss, malaise

**SIGNS**
- Typical joint involvement – MCP, PIP, wrists, feet, ankles, knees
- Typical joints spared – lumbar and thoracic spine, DIPs
- Articular findings – ulnar deviation, swan neck (MCP flexion, DIP flexion, PIP hyperextension) and boutonniere deformities (DIP hyperextension, PIP flexion), cock-up deformities (toes)
- C1-C2 instability
- Extra-articular manifestations
  - Skin – rheumatoid nodules, Raynaud’s, pyoderma gangrenosum, cutaneous vasculitis
  - Pulmonary – ILD, pleuritis, effusions, nodules
  - Cardiovascular – pericarditis, myocarditis, atherosclerosis/MI, AF, vasculitis
  - Neuro – mono/polynueuritis multiplex, CNS vasculitis, stroke
  - Ocular – scleritis, episcleritis, keratoconjunctivitis sicca
  - Heme – anemia, neutropenia, amyloidosis
  - Renal – glomerulonephritis, nephrotic syndrome
  - Vasculitis

**INVESTIGATIONS**
- Bloodwork – elevated ESR and CRP, positive RF (in 70% of pts), positive anti-CCP (in 80% of pts, more specific >90%)
- Radiographic findings – periarticular osteopenia, bone erosions, joint subluxation
- Increasing use of MSK U/S to diagnose synovitis and erosive disease
- Synovial fluid analysis – inflammatory findings

### MANAGEMENT

- At diagnosis start both rapid-acting agent to decrease inflammation and Disease-Modifying Anti-Rheumatic drug (DMARDs) – takes 1-3 mo for max effect
- Rapid-acting drugs – NSAIDs or COX-2 inhibitors or glucocorticoids or NSAIDs + glucocorticoids
- DMARDs – Methotrexate (+folic acid), Leflunomide or Sulfasalazine
  - If inadequate response to DMARDs after 3 mo consider adding another DMARD or biologic agent
- Biologics – anti-TNF agent is 1st line

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## Osteoarthritis

### OSTEOARTHRITIS

### DEFINITIONS

- Progressive deterioration of articular cartilage and surrounding joint structures
- Pathogenesis involves degenerative changes, “wear and tear” of the joints. Most common arthropathy and prevalence increases with age

### SYMPTOMS

- Joint pain, exacerbated by movement, relieved by rest
- Short duration of stiffness (<1/2h) after immobility
- Joint instability or buckling or locking
- Loss of function of the joint

### SIGNS

- Typical joint involvement: hip, knees, spine, 1st CMC, DIP and PIP
- Typical joint spared: MCP, shoulder, elbow, wrist
- General – Joint line tenderness, stress pain, joint effusion, crepitus on passive ROM, decreased ROM, mild inflammation
- Articular findings – Osteophytes can be in the DIP (Heberden’s nodes) and PIP (Bouchard’s nodes)

### INVESTIGATIONS

- Bloodwork – Unremarkable CBC, ESR and CRP
- Radiographic findings – joint space narrowing, subchondral sclerosis, subchondral cysts and osteophytes
- Synovial fluid analysis – non-inflammatory findings

### MANAGEMENT

- Non-pharmacological management – weight loss, PT, OT
- Pharmacological management
  - 1st line – acetaminophen/NSAIDs
  - Joint injections – corticosteroid, hyaluronic acid
- Surgical treatment – joint debridement, osteotomy, total or partial joint replacement
# Septic Arthritis

## SEPTIC ARTHRITIS

### ETIOLOGY

- **Bacterial** – gonococci, S. aureus, Streptococcus, Lyme, Brucellosis, Enterobacteriaceae, Mycobacteria (Pott’s disease)
- **Viral** – parvovirus, HBV, HCV, HIV
- **Fungal** – candida, coccidiomycosis, histoplasmosis
- *S. aureus is the most common cause of bacterial infection in all age groups*
- *In young and sexually active patients consider Gonococci infection*
- *In neonates and the elderly consider gram-negative organisms*

### SYMPTOMS

- Acute onset monoarticular arthritis
- Location (any joint can be affected) – Knee (most common), hip, wrist, shoulder, ankle
- Constitutional symptoms – Fevers, rigors, sweat, malaise, myalgias, pain
- Risk factors – immunocompromised host (DM, HIV, elderly, steroid use), damaged joints (OA, RA, surgery/prosthesis, gout, trauma), bacterial seeding (bacteremia secondary to IVDU, endocarditis or skin infection)

### SIGNS

- Vitals – fever, tachycardia
- Swollen, erythema and pain of the joint with both passive and active ROM
- Infection can form fistulae, abscesses or osteomyelitis
- *Note history and physical exam have poor sensitivity and specificity for septic arthritis, arthrocentesis should be performed as soon as suspected*

### INVESTIGATIONS

- CBC – leukocytosis
- ESR, CRP – elevated
- Blood Cultures – positive
- CT or MRI if suspect hip infection or epidural abscess
- Arthrocentesis
  - Cell count with differential – WBC usually >50,000, but can be < 10,000, >90% PMNs
  - Gram stain and culture, culture positive in >90%
  - Crystal – may still have concurrent infection if crystals found

### MANAGEMENT

- Begin prompt empiric antibiotics guided by Gram stain after surgical drainage
- IV antibiotics for ≥ 2 wks followed by oral antibiotics
  - IV Cefazolin or IV Cloxacillin
  - if MRSA risk factors or suspected IVDU or clinically unwell, add IV Vancomycin
  - if suspected Gonococcal infection – IV Ceftriaxone
- Surgical consultation as joint may require drainage and serial synovial fluid analysis should show declining WBC
# Crystal Arthritis

## GOUT

### DEFINITIONS
- Monosodium urate crystal deposition in joints which leads to inflammation
- Caused by uric acid under excretion (i.e. diuretics, decreased renal function, obesity) or uric acid overproduction (i.e. meat, seafood, alcohol, psoriasis, myeloproliferative disease, cytotoxic drugs, genetic variants)

### SYMPTOMS
- Sudden onset of pain classically in the 1<sup>st</sup> MTP ‘podagra’, pain can be at night
- Acute flares will subside in days to weeks
- Subsequent presentations may be polyarticular

### SIGNS
- Swollen, painful, erythema of the joint with decreased ROM
- Tophi – urate deposits commonly on first MTP, ear helix, olecranon bursae, tendon insertions
- Can be associated with gouty nephropathy or uric acid nephrolithiasis

### INVESTIGATIONS
- Synovial fluid analysis – needle-shaped, negatively birefringent crystals
- Radiographic findings – erosions with overhanging edge
- Elevated serum uric acid is NOT diagnostic for gout. Patients with gout can have normal serum uric acid levels.

### MANAGEMENT

#### ACUTE TREATMENT
- NSAIDs (avoid in CKD, CVD, risk of gastritis/GIB)
- Colchicine 1.2mg then 0.6mg BID ( risk of N/V/diarrhea, BM suppression, myopathy, neuropathy, requires renal dosing)
- Consider prednisone 0.5mg/kg/d for 5-10 days if no improvement or polyarticular

#### CHRONIC TREATMENT
- Lifestyle modifications – decreased intake of meat, seafood, increase intake of low-fat dairy products, weight loss, avoid dehydration
- Pharmacological prophylaxis – continue medications started for acute flare for 6 months if frequent attacks and if starting urate-lowering medication
- Urate-lowering medication –
  - Allopurinol – 1<sup>st</sup> line (rash, hypersensitivity syndrome, diarrhea, BM suppression, hepatitis, monitor CBC and LFT)
  - Febuxostat – 2<sup>nd</sup> line (monitor LFT, rash, arthralgia, nausea)

## CALCIUM PYROPHOSPHATE DEHYDRATE DEPOSITION (CPPD OR PSEUDOGOUT)

### DEFINITIONS
- Deposition of CPPD crystals within tendons, ligaments, articular capsules, synovium cartilage
- Usually idiopathic but if CPPD <50 yo consider metabolic causes (i.e. hemochromatosis, hyperparathyroidism, hypomagnesemia), joint trauma or familial chondrocalcinosis

### SYMPTOMS
- Mono or asymmetric oligoarthritis often involving the knees, wrist, MCP and rarely axial (indistinguishable from gout except through synovial fluid exam for crystals)

### SIGNS
- Swollen, painful, erythema of the joint with decreased ROM
INVESTIGATIONS

- Synovial fluid analysis – rhomboid-shaped, weakly positive birefringent crystals
- Radiographic findings – chondrocalcinosis seen as punctate linear densities in articular cartilage, menisci, fibrocartilage of wrist, hands, pubic symphysis
- Bloodwork – Ca, Mg, Fe, ferritin, TIBC, uric acid, PTH if age < 50yo

MANAGEMENT

- Acute treatment – same treatment as gout, if associated with metabolic disease treat this
- Chronic treatment – low dose daily colchicine or NSAIDs may be effective for prophylaxis or chronic arthropathy

References