Mastering The Boards and Clinical Examinations In Internal Medicine

HEMATOLOGY, NEPHROLOGY & INFECTIOUS DISEASES

A.B.R. Thomson

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2016

THE WESTERN WAY

Medical drawings by S. Lee and E. Howell

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MASTERING THE BOARDS AND THE CANMED OBJECTIVES

Medical expert

The discussion of complex cases provides the participants with an opportunity to comment on additional focused history and physical examinations. They should provide a complete and organized assessment. Participants are encouraged to identify key features, and develop themselves an approach to problem–solving.

The case discussions, as well as the discussion of cases around a diagnostic imaging, pathological or endoscopic bases, provide the means for the candidate to establish an appropriate management plan based on the best available evidences to clinical practice. Throughout, an attempt is made to develop strategies for diagnosis and development of clinical reasoning skills.

Communicator

The participants demonstrate their ability to communicate their knowledge, clinical findings, and management plan in a respectful, concise and interactive manner. When the participants play the role of examiners, they demonstrate their ability to listen actively and effectively, ask questions in an open–ended manner, and provide constructive and helpful feedback in a professional and non–intimidating manner.

Collaborator

The participants use the "*you have a green consult card*" technique of answering questions as fast as they could, and interact with other health professional participants to move forward with the discussion and problem–solving. This helps the participants to build upon what they have already learned about the importance of collegial interaction.

Manager

The participants are provided with assignments in advance of the three–day GI Practice Review. There is much work for them to complete before, as well as afterwards, so they learn to manage their time effectively, and to complete the assigned tasks proficiently and on time. They learn to work in teams to achieve answers from small group participation, and share this with other small group participants through effective delegation of work. Some of the materials need the access to information technology effectively for them to access information that will help to facilitate the delineation of adequately broad differential diagnoses, as well as rational and cost–effective management plans.

Health advocate
In answering the questions and case discussions, the participants are required to consider the risks, benefits, costs and impacts of each investigations and therapeutic alliances upon the patient and their loved ones.

Scholar
By committing to the pre– and post–study requirements, plus the intense three–day active learning Practice Review with colleagues is a demonstration of commitment to personal education. Through the interactive nature of the discussions and the use of the "*green consult card*", they reinforce their previous learning in the importance of collaborating and helping one another to learn.

Professional
The participants are coached how to interact verbally in a professional setting, being straightforward, clear and helpful. They learn to be honest when they cannot answer questions, make a diagnosis, or advance a management plan. They learn how to deal with aggressive or demotivated colleagues, how to deal with knowledge deficits, how to speculate on a missing knowledge byte by using first principals and deductive reasoning. In a safe and supportive setting, they learn to seek and accept advice, to acknowledge awareness of personal limitations, and give and take 360^{o} feedback.

Knowledge
The basic science aspects of gastroenterology are considered in an adequate detail to understand the mechanisms of diseases, and the basis of investigations and treatment. In this way, the participants respect the importance of an adequate foundation in basic sciences, the basics of the design of clinical research studies to provide an evidence–based approach, the designing of clinical research studies to provide an evidence–based approach, the relevance of their management plans being patient–focused, and the need to add "compassionate" to the Three Cs of Medical Practice: competent, caring and compassionate.

"They may forget what you said, but they will never forget how you made them feel."

Carl W. Buechner, on teaching

"With competence, care for the patient. With compassion, care about the person."

Alan B. R. Thomson, on being a physician.

PROLOGUE

HREs, better known as, High Risk Examinations. After more than two decades of study, sacrifice, long hours, dedication, ambition and drive, we who have chosen Internal Medicine, and possibly through this subspecialty, we still have an HRE, the [Boards] Royal College Examinations. We have been evaluated almost daily by the sadly subjective preceptor–based assessments, and now we face the fierce, competitive, winner–take–all objective testing through multiple choice questions (MCQs), and for some, the equally challenging OSCE, the objective standardized clinical examination. Well, we know that in the real life of providing competent, caring and compassionate care as physicians, as internists, a patient is neither a MCQ nor an OSCE. These examinations are to be passed, a process with which we may not necessarily agree. Yet this is the game in which we have, thus, far invested over half of our youthful lives. So let us know the rules, follow the rules, work with the rules, and succeed. So that we may move on to do what we have been trained to do, do what we may long to do and that is to care for our patients.

The process by which we study for clinical examinations is different than the MCQs: not trivia, but an approach to the big picture, with thoughtful and reasoned deduction towards a diagnosis. Not looking for the answer before us, but understanding the subtle aspects of the directed history and focused physical examination, yielding an informed series of hypotheses, a differential diagnosis to direct investigations of the highly sophisticated laboratory and imaging procedures, now available to those who can wait, or pay.

This book provides clinically relevant questions in taking a history and performing a physical examinations, with sections on Useful background, and where available, evidence–based performance characteristics in rendering clinical skills. Just for fun are included "*So you want to be a such-and-such specialist!*" to remind us that one of the greatest strengths we can possess to survive in these times, is to smile and even to laugh at ourselves.

Sincerely,

Emeritus Distinguished University Professor, University of Alberta

Adjunct Professor, Western University

DEDICATION

To Pam Johnson

ACKNOWLEDGEMENTS

Patience and patients go hand in hand. So also does the interlocking of young and old, love and justice, equality and fairness. No author can have thoughts transformed into words, no teacher can make ideas become behavior and wisdom and art, without those special people who turn our minds to the practical – of getting the job done!

Thank you, Naiyana and Duen for translating those terrible scribbles, called *my handwriting*, into the still magical legibility of the electronic age. Thank you, Sarah, for your creativity and hard work.

My most sincere and heartfelt thanks go to the excellent persons at JP Consulting, and CapStone Academic Publishers. Jessica, you are brilliant, dedicated and caring. Thank you.

When Rebecca, Maxwell, Megan Grace, Henry, Felix, Toby and Grady ask about their Grandad, I will depend on James and Anne, Matthew and Allison, Jessica and Matt, and Benjamin to be understanding and kind. For what I was trying to say and to do was to make my professional life focused on the three Cs – competence, caring, and compassion – and to make my very private personal life dedicated to family – to you all.

DISCLAIMER

The primary purpose of this publication is education. The author, editor and publisher acknowledge that the development of new material opens its way for possible errors – what is correct today might not be the standard of care tomorrow. Readers are advised to ensure that the doses of drugs which they use are in compliance with their country's product information, and that the use of any therapeutic agent, be it a pharmaceutical or a technology, should be guided by local guidelines. There is often a wide diversity of professional opinions. Guidelines from one country are not always congruent with another.

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Thank you

Alan Thomson

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HEMATOLOGY

TOUGH TIMES FOR THOSE OF YOU WHO NEVER LIKED MATH!

- Sensitivity (sens, or SN)

  $$\frac{\text{True–positive test results}}{\text{True–positive plus false–negative results}}$$

  SN out: Sensitive test that is Negative rules OUT disease

- Specificity (spec, or SP)

  $$\frac{\text{True–negative test results}}{\text{True–negative plus false–positive}}$$

  SP in: Specific test that is Positive rules IN disease
  Note: The prevalence of disease does not affect sens or spec, and does not affect LR (likelihood ratio; please see below)

- PPV (positive predictive value)

  $$\frac{\text{True-positive test results}}{\text{All positive}}$$

  Given a positive test result probability, the patient has the disease

- NPV (negative predictive value)

  $$\frac{\text{True–negative test results}}{\text{All negative}}$$

  Given a negative test result

  Note: ↑ prevalence of a disease → ↑ prevalence → ↓ NPV

- When plotting the receiver operator characteristic (**ROC**) curve, plot sensitivity (true–positive rate, as the y–axis) vs. 1-specificity (false–positive rate)
  - The best cut–off point for optimal balance between sensitivity and specificity will be closest to upper left corner of the plot
  - Test with highest accuracy, Greatest area–under the curve (**AUC**) of the ROC graph
- Positive likelihood ratio (PLR) = sens / 1– spec PLRs of 2, 5 and 10 ↑ probability of disease ~ 15%, 30%, 45%, respectively
- Negative likelihood ratio (NLR) = 1– sens / spec

  NLR of 0.5, 0.2 and 0.1 ↓ probability of disease ~ 15%, 30%, 45%, respectively

Note: PLR, NLR

- Independent of prevalence of disease
- Need to assess the pretest probability of having the disease
- Risk estimates

	Outcome	
Treatment	Positive	Negative
Yes	A	B
No	C	D

Absolute risk reduction (**ABR**) = [a / (a + b)] – [c / (c+d)]

Relative risk (**RR**) = [a / (a + b)] – [(c / c+d)]

Usually, odds ratio (OR) can be substituted for RR or ~ RR

AR, RR, or are estimates of cumulative risk over time, usually at the end of the study

Hazard ratio (HR) estimates the risk at a point in time (not cumulative, as is RR)

Number needed to treat (NNT) = 1 / ARR

"When you are transparent, there is no place to hide."

James Calvin

THROMBOTIC DISORDERS

To be considered here:

- Inherited thrombophilic conditions
  - Factor V Leiden (FVL)
  - Prothrombin G 20210 Gene Mutation (PGM)
  - Anti–thrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Dysfibrinogenemia
- Acquired thrombophilic conditions
  - Surgery
  - Trauma
  - Cancer
  - Anti–phospholipid syndrome (APS)

Inherited Thrombophilic Conditions

Thrombophilia

- Give the causes of inherited and acquired thrombophilias

  - Inherited thrombophilia
    - Prothrombin G20210A mutation
    - Anticoagulant deficiencies (anti–thrombin, protein C, protein S)
    - Selected dysfibrinogenemia

  - Acquired Thombophilia
    - Immune
      - Lupus anticoagulant or antiphopholipid antibody syndrome
    - Infiltration
      - Solid organ malignancy
      - Myeloproliferative diseases
    - Drugs
      - Estrogens (oral contraceptives, hormone replacement therapy)
    - Pregnancy
    - Obesity

- Travel
- Trauma
  - Trauma
  - Post–operative state
- Senescence
- Idiopathic
- Paroxysmal nocturnal hemoglobinuria (PNH)

- Mixed Risk Factors
  - Hyperhomocysteinemia
  - Elevated levels of factors VII, IX, & XI

Adapted from: Ghosh, A.K. *Mayo ClinicScientific Press* 2008, Table 11-19, 454.

- Give 5 conditions associated with thrombophilia and thrombosis.
  - Common
    - Factor V Leiden
      - Most common inherited thrombophilia (in Caucasian)
    - Mutation of prothrombin gene
    - Anti–phospholipid syndrome
  - Less common
    - Protein C
    - Protein S
    - ↑ homocysteinemia
    - ↓ anti–thrombin

- Give the conditions under which testing for thrombophilic disorder is appropriate and inappropriate.
  - Appropriate
    - Idiopathic DVT
      - First episode
      - < 50 years
    - Recurrent DVT
    - Family history
      - First–degree relative < 50 year with history of idiopathic thrombosis
  - Inappropriate
    - Not fulfilling above “appropriate” indications
    - During an acute thrombotic event
    - < 2 weeks after stopping anticoagulation

Useful background:

- Causes of purpura
  - ↓ platelets
    - marrow aplasia
  - abnormal vessel wall
    - Senile purpura
  - drugs
    - steroids
    - anticoagulants

- Vascular defects
  - Senile purpura
  - Steroid–induced purpura
  - Henoch–Schönlein purpura
  - Scurvy
  - Von Willebrand's disease
  - Uremia

- Coagulation defects
  - Hemophilia
  - Anticoagulants
  - Christmas disease

Adapted from: Baliga, R.R. *Saunders/Elsevier* 2007, page 391.

Factor V Leiden (FVL)

- Definition
  - The FVL mutation disrupts the first of three activated protein C (APC) cleavage sites, slowing the degradation of activated factor V (factor Va) and factor VIIIa causing a marked increase heterozygotes and homozygotes in the risk of venous non–arterial thromboembolism (VTE). (MKSAP 16, Hematology and Oncology, 2012, page 53).
  - Further ↑ risk
  - Combined heterozygosity (i.e. with prothrombin G20210A gene mutation or PGM)
  - Oral contraceptive pill (OCP)
  - Travel

- What is the treatment of choice for VTE in the post-operative state?
  - Normal renal function - IV low molecular weight heparin; renal clearance (LMWH)
  - Abnormal renal function - IV unfractionated heparin (UFH), reticuloendothelial system (RES) clearance

- What anticoagulant is used for long–term anticoagulation of VTE?
  - Cancer - Low molecular weight heparin (LMWH) for 3 months or until cancer becomes inactive
  - No cancer - Warfarin
  - Unfractionated heparin (UFH) is not recommended for long–term anticoagulation in patient with active cancer

Prothrombin G20210A GENE Mutation (PGM)

- Definition
  - "PGM stabilizes prothrombin mRNA, increasing prothrombin protein levels by 30% and 70% in heterozygotes and homozygotes…..", thereby increasing the risk of venous thromboembolism (VTE) (MKSAP 16, Hematology and Oncology, 2012, page 53).
- Heterozygosity for both FVL and PGM approximately triples the risk of VTE, and the risk is further increased by acquired or lifestyle factors
- Diagnosis
  - DNA

Anti–thrombin Deficiency

- Definition
- Deficiency of thrombin, an endogenous anti–thrombotic protein, leads to reduced inhibition of serine proteases (i.e. thrombin, factor Xa), leading to ↑ risk of initial and recurrent VTE

- Subtypes of ATD

Type of ATD	Mutation defect	Risk
I	↓ protein synthesis	High
IIa	Thrombin–binding sites	
IIb	Heparin–binding sites	Low

Protein C deficiency

- Definition
  - Deficiency of protein C, which is a serine protease that inactivates factors Va and VIIIa, leads to ↑ risk of initial and recurrent VTE.

- Types

	Mutation	Effect of mutation
I	↓ protein C synthesis	↓ protein C activity ↓ protein C antigen
II	Altered protein function	↓↓↓ protein C activity ↓ protein C antigen

Protein S Deficiency

- Definition
  - Protein S deficiency leads to
    - ↓ degradation by protein C factors Va and VIIIa
    - ↓ inactivation of factors Xa by the inhibitor tissue factor pathway

Dysfibrinogenemia

- Definition
  - Mutations in the Aα, Bβ or gamma fibrinogen genes causing ↓↓↓ fibrinogen activity and ↓ fibrinogen antigen resulting in ↑ risk of thrombosis and bleeding

Acquired Thrombophilic Conditions

- Risks
  - Surgery
    - ↑ risk of VTE
      - Outpatient 10x
      - Inpatient 70x
    - ↑ risk
      - Higher first 3 months post–surgery
      - Persistent risk for 12 months
    - Types of surgery
      - Orthopedic
      - Trauma
      - Cancer
  - Benefit of prophylactic anticoagulation
    - ↓ risk of VTE by 60%
  - Trauma
    - ~ 60% develop deep vein thrombosis (DVT), 4% pulmonary embolus (PE), especially spinal cord or pelvic injury
  - Cancer
    - Pathogenesis
      - Cancers may:
    - Express tissue factor
    - Induce tissue factor by endothelial cells and monocytes
    - ↑ risk of VTE by 4- to 20- times
    - Risk highest with
      - Pancreatic and brain tumors
      - Metastatic disease
    - Continue anticoagulation for 3 – 6 months or until active disease is eradicated

Anti–phospholipid Syndrome

- Most common acquired thrombophilia

- Definition
  - Primary or secondary autoimmune disorder characterized by the presence of antibodies against phospholipids or phospholipid proteins, and causing venous, arterial or microvascular thrombosis by:
    - ↑ expression of tissue factor
    - ↑ activation of:
      - Platelets
      - Complement cascade

  ↓ function of protein C and anti–thrombin

- Pathogenesis
  - Antibody to B2–glycoprotein 1 bound to a phospholipid

- Clinical
  - Thrombosis
  - Pregnancy ↑ morbidity
  - Skin necrosis within 5 days of starting warfarin
  - Venothrombolic, arteriothrombolic or microvascular embolus (disseminated microvascular thrombosis and multiorgan failure → catastrophic APS)
  - Adverse pregnancy outcome:

  ≥ 3 unexplaned, consecutive spontaneous abortions before week 10

  ≥ 1 unexplained fetal deaths beyond week 10

  ≥ 1 premature births before week 34 because of preeclampsia, eclampsia or placental insufficiency

- Laboratory
  - Lupus anticoagulant
  - Antibody to cardiolipin (a phospholipid)
  - Antibody to B2 glycoprotein I (a phospholipid binding protein)

Please see standard Internal Medicine textbook, UpToDate, or current review such as MKSAP 16, Hematology and Oncology, 2012, Table 26, page 55 for details of diagnostic criteria for anti–phospholipid syndrome.

- Diagnosis
  - ≥ 1 clinical criteria
    - Vascular thrombosis
    - Pregnancy morbidity
  - ≥ 1 lab' criteria
    - Lupus anticoagulant
    - Anti–cardiolipin antibody
    - Anti–B2–glycoprotein 1 antibody

- Give the criteria for diagnosis of anti-phospholipid syndrome.

Clinical	– Venous or arterial thromboembolism (VTE or ATE) – Pregnancy morbidity ≥ first trimester miscarriage or one fetal death	
Laboratory	– Dilute Russell's viper venom time anti–cardiolipin antibody assay B2–glycoprotein I antibody assay	Positive on 2 occasions at least 12 weeks apart

- Treatment

A patient with an inherited thrombophilic disorder such as factor V Leiden, or an acquired thrombophilic disorder such as anti–phospholipid syndrome, is placed on long–term oral therapy with an anticoagulant. Within the first few days of receiving warfarin (especially high doses), skin necrosis develops.

- Give the pathogenesis of skin necrosis which occur when patient with thrombophilia is given an oral anticoagulant such as warfarin.
  - An oral anticoagulant, i.e. warfarin, especially when given in high dose, will rapidly deplete protein C
  - This rapid depletion of protein C causes a hypercoagulable state
  - The hypercoagulable state leads to thrombosis and skin necrosis

- Initiate UFH / LMWH, with dose–adjusted to level of anti–Xa if ↑ aPTT
- Maintain target INR of 2 – 3 using warfarin
- For recurrent VTE / ATE despite the use of warfarin
  - LMWH
  - Fondaparinux

Abbreviations: aPTT, activated partial thromboplastin time; ATE, arteriothrombotic embolism; LMWH, low molecular weight heparin; UFH, unfractionated heparin; VTE, venothrombotic embolism

- For catastrophic APS plus multiorgan failure
  - Resume anticoagulation, if stopped
  - Corticosteroids, high dose
  - Intravenous immunoglobulin (IVIG)
  - Plasma exchange (PE)
  - Mortality ~ 50%, despite therapy above

Pregnancy

- Give the pathophysiology of the hypercoagulable state in pregnany.

  - In pregnancy, there is:
    - ↑ factor VIII activity
    - ↑ von Willebrand factor
    - ↑ Cyb–binding protein
  - The ↑ C4b–binding protein results in more bound protein S and less free protein
  - The ↓ free protein S causes ↓ protein S activity, thus ↑ coagulability

Acquired Thrombophilic Disorders in Other Diseases

- What are the laboratory changes seen in 4 conditions associated with acquired thrombophilic disorders?

	Anti–thrombin deficiency	Protein C deficiency	Protein S deficiency	Dysfibrinogenemia
Liver disease		+		
Nephrotic syndrome	+			
Pregnancy			+	
AC Rx		+		
Acute thrombosis		+		
Liver cancer				+

ACQUIRED COAGULATION FACTOR DEFCIENCY

- Give the causes of acquired coagulation factor deficiencies.
    - Vitamin K–dependent factors
        - Warfarin
        - Decreased nutritional intake or Malabsorption
    - Factor V
        - Myeloproliferative disease
    - **Von Willebrand Factor & Factor VIII**
        - Aquired von Willebrand syndrome
    - Factor X
        - Amyloid
    - Multiple factors
        - Liver failure
        - Disseminated intravascular coagulation (DIC)

Adapted from: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, page 450.

Vitamin K Deficiency

- Vitamin K–dependent coagulation factors are II, VII, IX and X
- A malnourished patient with cirrhosis who is on maintenance antibiotic for the prevention of spontaneous bacterial peritonitis (SBP) develops pulmonary embolus.

VENOTHROMBOTIC EMBOLISM

D–dimer, DUS and Wells Score to Diagnose DVT

Step 1. Determine the diagnostic probability of DVT
Wells score ≤ 0 (low pretest probability)
↓
D–dimer → negative → DVT unlikely, no further testing
→ proximal duplex ultrasonography (DUS), CTA or MRA

Abbreviations: CTA, CT angiography; DVT, deep venous thrombosis; MRA, MR angiography

For details on the Wells clinical deep venous thrombosis model, please see standard medical tests, or recent reviews such as MKSAP 16, Hematology and Oncology 2012, Table 28, page 57.

Anticoagulation Prophylaxis for venothrombotic embolism (VTE)

- Assess VTE for prophylaxis use

Age	– > 60 years
CNS	– NYHA class III / IV heart failure
Lung	– Acute respiratory failure – History of venous thromboembolism (VTE)
Hematology	– Thrombophilia
GI	– Inflammatory bowel disease (IBD)
MSK	– Acute rheumatic disease – Immobility
Cancer	– "Active" or being treated
Infection	– Acute
Surgery	

- Chose LMWH for:
  - CVA
  - Active cancer
  - Surgery
  - Trauma
- Choose UFH
  - Renal failure (creatinine < 30 mL/minute)
- Non-pharmaceutical options
  - Intermittent pneumatic devices
    - Prophylaxis indicated, but anticoagulation is contraindicated
  - Vena cava filter (VCF)
  - Thrombolysis
    - Catheter
    - Directed pharmacomechanical
  - Surgical thrombectomy
    - For extremity thrombosis
- Stopping rules for warfarin
  - Usual practice – At discharge from hospital
  - Hip arthroplasty or fracture surgery – ~ 30 days post–op
  - Knee arthroplasty – ~ 30 days
  - Abdominal or pelvic surgery – ~ 30 days
  - Major trauma – When in–patient rehabilitation completed

- There is a ↑ risk of recurrence of idiopathic VTE (50% in 10 years). Give 2 factors which suggest that patients with idiopathic VTE require long–term anticoagulation.
  - ↑ D–dimer on and after anticoagulation is stopped
  - Persistent thrombosis on duplex ultrasound (DUS)

- When will a retrievable filter should be placed with a vena cava filter?
  - No likelihood for future anti-coagulation → no retrievable filter needed

A NEW TEACHING

Superficial vein thrombophlebitis → duplex ultrasonography

↓

- Proximal greater saphenous vein thrombosis
- > 5 cm superficial thrombosis

↓

- Anticoagulation, plus
- NSAIDs, and
- Compression stockings

CLINICAL GEM

- Give the safety of warfarin during pregnancy.
  - During the first trimester, do **not** give warfarin → embryopathy
  - For anticoagulation as prophylaxis of VTE in pregnancy especially during the 1st trimester, use prophylactic or intermediate dose of low molecular weight heparin (LMWH)

- What dose of warfarin is use to start anti-coagulation therapy?
  - Start with very low dose of warfarin, i.e. 1 mg/day

➢ Examples of drug interactions with warfarin
  - Direct gastrointestinal injury (i.e. non–steroidal anti–inflammatory drugs)
  - Altered gut Vitamin K synthesis (i.e. antibiotics)
  - Altered warfarin metabolism (i.e. cotrimoxazole, metronidazole, fluconazole, amiodarone)
  - Interference with vitamin K cycle (i.e. acetaminophen)
  - Altered platelet function (i.e. acetylsalicylic acid, clopidogrel)

Source: Juurlink, D. *CMAJ* 2007; 177: 369-371.

Anticoagulant Drugs

Heparin

- Mechanism
  - Binding of heparin to anti–thrombin → ↑ inhibition of activated serine proteases (i.e. Xa, thrombin)
  - Metabolism UFN
    - Degradation by:
      - Endothelial cells
      - Macrophages
    - Renal elimination
  - Dosing based on weight
    - Monitor aPTT
  - LMWH (enoxaparin)
    - Renal elimination
    - T1/2 ~ 5 hours
  - Weight–based dosing, with no need to follow–up aPTT
  - Reversal protamine
    - For UFH 1 mg

Fondaparinux

- Catalyzes anti–thrombin inhibition of factor Xa
- Renal excretion
- T1/2 ~ 18 hours
- Reversal

IV–recombinant human factor VIIa

Warfarin

- Mechanism of action
  - ↓ hepatic vitamin K oxide reduction → ↓ synthesis of factor II, VII, IX and X, as well as proteins C and S
  - Effect of vitamin K on oxide reductase is insufficient by cytochrome P–450 enzymes in the microsomes

- For a list of medications which ↑ or ↓ INR, refer to standard medical texts, UpToDate, or recent reviews such as MKSAP 16, Hematology and Oncology 2012, Table 30, page 58.

- Give the classes of drugs that interact with warfarin ("8 As").

Drugsor drug classes	Risk of hemorrhage	Mechanisms
○ **A**ntibiotics		
– Most agents, but especially cotrimoxazole, metronidazole, macrolides and fluoroquinolones	↑	↓ vitamin K synthesis ↓ hepatic warfarin metabolism
– Rifampin	↓	↑ cytochrome P–450 (CYP)
○ **A**ntifungals		
– Fluconazole, miconazole	↑	↓ CYP–2C9
○ **A**ntidepressants		
– Serotonergic agents (selective serotonin reuptake inhibitors [SSRIs])	↑	↓ primary hemostasis (may also inhibit CYP–2C9)
○ **A**ntiplatelet agents		
– Acetylsalicylic acid, clopidogrel, ticlopidine	↑	↓ primary hemostasis
○ **A**miodarone	↑	↓ CYP 2C9
○ **A**nti–inflammatory agents		
○ All, including selective NSAIDs, Coxibs	↑	↑ mucosal injury ↓ primary hemostasis
○ **A**cetaminophen	↑	↓ vitamin K cycle
○ **A**lternative remedies		
– *Ginko biloba*, dong quai, fenugreek, chamomile	↑	Multiple, and often incompletely characterized
– St. John's wort	↓	Multiple and often incompletely characterized

Adapted from: David, N.J. *CMAJ* 2007; 177(4): 369-371, Table 1, page 370.

- Reversal of warfarin anticoagulation in life–threatening bleeding
  - Stop warfarin
  - IV vitamin K 10 mg over 1 hour, plus
  - Fresh frozen plasma (FFP) IV, plus
  - Prothrombin complex concentrates (PCC), 3–factor PPC with FFR, or recombinant factor VII, or 4–factor PPC

THROMBOCYTOPENIA

- Definition
  - Platelet count < 150 x 10^9/L (< 150,000/μL)

- Causes: mechanisms
  - ↓ production
    - Congenital
    - Nutritional deficiencies
    - Infection
    - Inflammation or autoimmune
    - Infiltration
    - Hematological malignancy
    - Hemolysis
    - Aplastic anemia
    - Myclodysplasia
    - Drugs
      - Alcohol
      - Chemotherapy
    - Falconi anemia
  - ↑ destruction
    - Immune–mediated
    - Non–immune–mediated
  - Splenic sequestration
    - Splenomegaly

- Clinical caution
  - Platelet count

< 150,000/μL (< 150 x 10^9/L)	Thrombocytopenia
30– to 40,000/μL	Idiopathic or immune thrombocytopenic purpura (ITP)
20– to 50,000/μL	↑ risk of mucocutaneous bleeding
< 10,000/μL	↑ risk of intracranial bleeding

- Give the importance of platelet clumping in patients with thrombocytopenia.
    - Clumping of platelets leads to the laboratory error in which the platelets in clumps are not counted, leading to pseudothrombocytopenia.

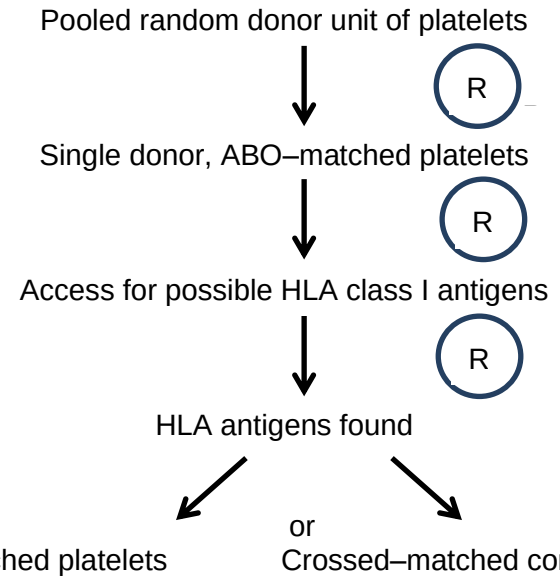
Refractoriness to Platelet Transfusion

- Definition
    - Failure of platelet count to increase by > 10 x 10^9/L (> 10,000/μL) for each unit of platelets transfused

- Causes
    - Non–immune
        - Fever
        - DIC
        - Drugs
    - Immune
        - Alloimmunization

Abbreviations: DIC, disseminated intravascular coagulation

- Treatment



Ⓡ, refractoriness of platelet transfusion (failure of platelet count to increase by > 10 x 10^9/L (> 10,000/μL)

Immune or "**idiopathic**"] **thrombocytopenic purpura (ITP)**

- Definition
  - "….an acquired autoimmune condition in which autoantibodies are directed against platelet surface proteins, leading to platelet destruction that may partially counteracted by increased bone marrow platelet production" (MKSAP 16, Hematology and Oncology, 2012, page 49).
  - ITP is a diagnosis of exclusion: for thrombocytopenia occurring in pregnancy, consider:
    - Gestational thrombocytopenia
    - Preeclampsia
    - HELLP
    - DIC
    - TTP

Abbreviations: HELLP, hemolysis elevated liver enzymes low platelet count; DIC, disseminated intravascular coagulation

- Causes
  - Ideopathic
  - Immune (i.e. systemic lupus erythematosus [SLE])
  - Infection (e.g., HIV)
  - Infiltration or lymphoproliferative malignancy
  - Iatrogenic
    - Drugs
- Treatment
  - Indications — Bleeding, or Platelets < 30-40,000/μL
- ITP in pregnancy – please see page 139

- Corticosteroids
  - Dexamethasone 40 mg/day for 4 days, then
  - Prednisone or methylprednisolone 1-2 mg/kg per day
  - Intravenous immunoglobulin (IV–IG)
  - Anti–D immunoglobulin
  - Immunosuppression
  - Rituximab

  - Mycophenolate mofetil (MPM)
    ↓ Failures
  - Stimulate thrombopoietin receptor to ↑ production of bone marrow megakaryocytes (delayed HIT)
    ↓
    Splenectomy

Heparin–induced thrombocytopenia (HIT) and heparin–induced thrombocytopenia with thrombosis (HITT)

- Definition
  - 5 to 10 days after exposure to heparin, or at ≤ 1 day ↓ platelets if there has been prior heparin exposure within last 30 days (delayed HIT) risk of HIT is ↓ platelets by 50%, with individuals developing paradoxical arterial or venous thrombosis based upon their "4T score" (thrombocytopenia, timing of platelet fall, now thrombosis (or skin necrosis or acute systemic reaction), presence of other possible causes of thrombocytopenia, and 4T score interpretation

  - A platelet decrease of > 50% in patient taking heparin or a thromboembolic events 5 to 10 days after starting heparin" (Board Basics 2013, page 158)

  - Late onset may occur up to 3 weeks after stopping heparin

  - Recent exposure to heparin may accelerate HIT–onset upon reexposure to heparin (serotonin release assay)

- Laboratory

More sensitive	More specific
○ ELISA measurement of antibody against heparin: platelet factor 4 complex	– C^{14} – serotonin release assay – Heparin–induced platelet aggregation assay

Abbreviation: ELISA, enzyme–linked immunosorbant assay

- Process

Clinical suspicion

↓

Calculate "4T" score if score high probability of HIT (6 to 8)

↓

Sensitive lab test for HIT

- Diagnosis
  - Serotonin release assay (SRA) positive, but negative SRA does not exclude diagnosis
  - Anti–PF4 / heparin antibodies (high risk of false positives, ↓ specificity)
- Treatment
  - Stop heparin (do not use unfractionated heparin [UFH] or low molecular weight heparin [LMWH])
  - In place of heparin, substitute non–heparin anticoagulant
  - Lepirudin (do <u>not</u> use in renal disease)
  - Argatroban (do <u>not</u> use in liver disease)
  - Danaparoid
  - Bivalirudin for acute cardiac interventions
  - Do not use warfarin in place of heparin in HIT or HITT
  - Continue anticoagulation
    - Renal disease
    - No renal disease: lepirudin, argatroban, danaparoid
    - Do not use lepirudin (renal excretion)

- Stop heparin
- Switch to non–heparin alternative anticoagulant, i.e.:
  - Danaparoid
  - Lepirudin
  - Argatroban
  - Bivalirudin

  - Renal dosing
  - Hepatic dosing
  - Patient needs acute cardiac intervention

Thrombotic Thrombocytopenic Purpura (TTP)

- Definition
  - An autoimmune disorder characterized by the development of antibodies against the protease ADAM TS13, leading to the accumulation of high molecular weight multimers of von Willebrand factor (VWF), which then causes abnormal platelet adhesion and activation, thrombocytopenia, microangiopathic hemolytic anemia, as well as renal neurological and GI complications.
  - Note the association with hemolytic uremic syndrome (HUS)

- Clinical
  - Microangiopathic hemolytic anemia
    - Schistocytes, peripheral blood)
    - ↑ serum lactate dehydrogenase (LDH)
  - Renal complications
    - ↑ creatinine
    - Hematuria
    - Proteinuria
  - Neurological
    - Coma
    - Seizures
    - Stroke
  - GI
    - Pancreatitis
  - Associations
    - Pregnancy
    - HIV
    - HUS

- Laboratory (please see above definition)
  - ↓ ADAM TS 13 activity and ↑ inhibitor titre suggest ↑ risk of relapse
- Treatment
  - Potential life–threatening (10% mortality despite treatment)
  - Plasma exchange (PE)
  - Fresh frozen plasma (FFP) transfusion if any delay starting PE, or if patient's condition is worsening
  - Role of corticosteroids is not proven

Hemolytic Uremic Syndrome (HUS)

- Overlaps with and very similar to TTP
  - *E. coli* O157:H7
  - *Shigella*
- Differences between HUS and TTP
  - More renal than neurological complications
  - Often precipitated by infection
  - Associated with abnormalities in complement system

- Differential diagnoses of TTP–HUS
  - Malignant hypertension
  - HELLP syndrome and preeclampsia
  - Anti–phospholipid syndrome (APS)
  - Scleroderma renal crisis

- Treatment
  - Due to the high mortality of underdiagnosed TTP–HUS and delayed treatment with plasma exchange (PE), any patient with schistocytes in the peripheral blood, ↑ LDH and thrombocytopenia should be considered as a case of TTP–HUS, and PE should be started immediately

SO YOU WANT TO BE A HEMATOLOGIST!

- In a patient with purpura, what is Moschcowitz syndrome?
    - Speak English. Moschcowitz's syndrome is simply thrombotic thrombocytopenic purpura (TTP), an acute disorder characterized by:
        - Thrombocytopenic purpura
        - Microangiopathic hemolytic anemia
        - Transient and fluctuating neurological features
        - Fever
        - Renal impairment

Source: Baliga, R.R. *Saunders/Elsevier* 2007, page 391.

DISORDERS OF PLATELET FUNCTION

- Test for a defect in primary hemostasis when there is a personal and family history of mucocutaneous or post–surgical bleeding
- Limited testing availability
    - PFA–100® (Platelet Function Analyzer – 100)
    - Bleeding time (BT)
- ↑ BT
    - Platelet dysfunction
    - Von Willebrand disease (vWD)
    - Thrombocytopenia and anemia
    - Abnormal vascular contractility

Thrombocythemia

- Please see later description of essential thrombocythemia

Acquired Platelet Dysfunction

- Causes
  - Chronic renal disease
    - Treatment for acute bleeding
      - Desmopressin
      - Dialysis
      - Conjugated estrogens
  - Myeloproliferative and myeodysplastic syndromes (MMD)
    - Platelet transfusions
  - ASA and NSAIDs
  - Some foods, i.e. garlic, ginseng

In thrombocytopenia, there are buzzwords used on an MCQ which may be associated with the cause of the disorder.

- Give the likely cause of the thrombocytopenia when the following "buzzwords" are used.

Buzzwords	Suggested diagnosis on MCQ
o Schistocytes	– Disseminated intravascular coagulopathy (DIC) – Thrombotic thrombocytopenic purpura – hemolytic uremic syndrome (TTP–HUS) – Hmolysis, elevated liver tests, low platelets (HELLP)
o Teardrop-shaped RBCs	– Myeloplastic syndromes
o Hypersegmented neutrophils	– Deficiency of folate or cobalamin, causing thrombocytopenia
o Use or reuse of heparin o Thrombocytopenia plus thrombosis	– Heparin–induced thrombocytopenia (HIT)
o Blood transfusion	– Post–transfusion purpura thrombocytopenia

CLINICAL CLUES

A patient develops thrombocytopenia and purpura ≥ week after transfusion or after pregnancy. You suspect post–transfusion thrombocytopenia.

- Give the method of diagnosis and treatment for post–transfusion thrombocytopenia.
    - Antibodies to human platelet antigen (HPA–1a) confirms the diagnosis
    - Treat with IV–immunoglobulin

➢ Clinical

- Take a directed history of thrombocytopenia
    - Ideopathic
    - Dilutional
        - Massive transfusion or infusion
        - Pregnancy
    - ↑ destruction
        - Autoimmune
        - Drug–induced
        - Connective tissue diseases
        - Consumptive (DIC)
        - Sepsis
    - ↓ production
        - Anaplastic anemia
        - Metastatic disease
        - Hematologic malignancies (marrow replacement)
        - Nutritional
            - Vitamin B12 & folate deficiency
        - Viral infections (HIV, CMV, hepatitis)

Abbreviations: CMV, Cytomegalovirus; DIC, Disseminated intravascular coagulation; HIV, Human immunodeficiency virus

Adapted from: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, Table 11-17, page 452.

Thrombocytopenia in Pregnancy (Gestational Thrombocytopenia)

- A "physiological" effect of pregnancy is due to:
  - ↑ blood volume → dilutional thrombocytopenia
- Suspect pathological cause of thrombocytopenia
  - If platelets < 50 x 10^9/L (50,000/μL)
  - If ↓ platelets in T1 or T2 (first or second trimesters)
  - When platelet count falls in trimester 2/3, the diagnosis is usually gestational thrombocytopenia, preeclampsia, or HELLP.
  - These must be differentiated because early delivery is the treatment.
  - Other causes of thrombocytopenia are treated the same as in a non–pregnant patient.
    - TTP–HUS
    - ITP
    - DIC

C	T1	T2	T3	Postpartum
	← TTP – HUS →		Preeclampsia	preeclampsia
	↓		↓ ~ 10%	
	MAHA		HELLP	
	Thrombocytopenia		AFLP	
	↓		↓	
	PE		Delivery	

Abbreviation: AFLP, acute fatty liver of pregnancy; C, conception; HELLP, hemolysis elevated liver enzymes low platelet count; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; T, trimester; TTP, thrombotic thrombocytopenic purpura

PT / aPTT	MAHA	↓ platelets	PT/aPTT	DIC	↓ BS	↑ SBP	Proteinuria	LE
Preeclampsia	-	-	-	-	-	+	+	↑
HELLP	+	+	N	-	-	+/-	+	+
TTP-HUS	+	+	-	-	-	-	-	-
AFLP	-	-	↑	+	+	-	-	↑

Abbreviations: AFLP, acute fatty liver of pregnancy; aPTT, activated partial thromboplastin time; BS, blood sugar; DIC, disseminated intravascular coagulation; HELLP, hemolysis elevated liver enzymes low platelet count; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura

CLINICAL CLUES

- Preeclampsia
  - Half occur T3, ~ half postpartum
  - 10% progress to HELLP
- HELLP
  - Half have hypertension
  - Half are normotensive

- Treatment target
  - When to give platelets in pregnancy
    - Asymptomatic, PI < 50,000/µL
    - Symptomatic, < 30 – 40,000/µL
    - Cesarean section, < 50,000/µL
    - Neuraxial anesthesia, < 80,000/µL
  - Thrombocytopenia in neonate
    - Anti–platelet antibodies may cross the placenta
    - Thrombocytopenia in neonate ~ 10%
    - Problems with measuring fetal platelet levels
      - Scalp vein sampling is misleading

- Umbilical cord sampling may cause miscarriage (1%)

BLEEDING DISORDERS

CLINICAL GEMS AND PEARLS

Commonest causes

- ↑ PT
  - Vitamin K deficiency, including warfarin
  - Liver disease
  - DIC
  - Factor VII deficiency, acquired
- ↑ aPTT
  - Lupus inhibitor
  - Hemophilia

- Give the reason why the citrate–containing tubes must be filled at phlebotomy.
  - Less than complete filling of the collection tubes results in an excess of citrate for the volume of plasma, and the PT and aPTT will be falsely high.

Abbreviation: PT, prothrombin time; aPTT, activated partial thromboplastin time

➢ Classification

The classification of congenital and acquired disorders of coagulation is beyond the scope of this book. The interested reader is referred to standard textbooks of Hematology, or the reviews such as MKSAP 16, Hematology, 2012, Table 22 pages 44-45.

- Give a simple classification of bleeding disorders.

- Primary
  - Formation of platelet plus at site of vascular damage
  - Failure
    - Bleeding gums, nose
    - Easy bruising
    - Menorrhea
- Secondary
  - The coagulation cascade begins when the site of vascular damage is expressed
  - Failure
    - Bleeding into muscles, joints
    - Delayed bleeding

- Failure of primary or secondary hemostasis → bleeding after
  - Surgery
  - Trauma
  - Childbirth

➢ Laboratory

- In a patient with both ↑ PT and ↑ aPTT, give the role of the thrombin clotting (TCT).
  - To determine if there is:
    - A thrombin inhibitor (i.e. heparin)
    - Hypo– / –dysfibrinogenemia

- Give the interpretation of a mixing study performed when there is ↑ aPTT.
  - Correction of aPTT with adding normal plasma
    - Factor deficiency
  - Incomplete correction of aPTT
    - Presence of an inhibitor

- Give the diagnostic methods used to identify a bleeding disorder.
  - PT
  - aPTT
  - Mixing study
    - Mix plasma from patient with normal plasma to differentiate deficiency vs. inhibitor of factors
    - Mixing study
      - Correct → factor deficiency
      - Does not correct → circulating (inhibitor) anticoagulant
  - Bleeding time
    - Platelet disorders
    - Integrity of vessel walls
  - Thrombin time tests
    - Fibrinogen → fibrin conversion
  - Fibrinogen, fibrinogen–degradation product, D–dimer test
    - ↑ fibrinolysis

- Give the PT, aPTT and the result of mixing studies of the following coagulation disorders.

Coagulation tests		Mixing study corrects	Abnormality Deficiencies
PT	aPTT		
↑	↑		Single or multiple
↑	N		VII
N	↑	Yes	VIII, IX, XI, XII
			XII without bleeding
N	↑	No	Circulating inhibitor (anticoagulant) – think of conditions, i.e. SLE
N	N / ↑		Think of VWD

Note: the expected changes with therapeutic anticoagulation

- Give the effect of treatment (Rx) with warfarin and UFH on PT, aPTT and mixing study correction.

Rx	PT	aPTT	Mixing study correction
○ Warfarin	↑↑	↑	
○ UFH	N	↑	Yes

Abbreviations: aPTT, activated partial thromboplastin time; N, normal; PT, prothrombin time; SLE, systemic lupus erythematosus; UFH, unfractionated heparin; VWD, Von Willebrand disease

Hemophilia A and B

- Definition
  - X–-linked recessive disorders due to deficiency of factor VIII (hemophilia) or factor IX (hemophilia B)

- Clinical
  - Hemarthrosis → joint degeneration
  - CNS bleeding
  - Bleeding after
    - Surgery
    - Trauma

  - X–linked disorders

Hemophilia	Factor Deficiency
A	VIII
B	IX

- Diagnosis
  - Normal, aPTT ↑, corrects with addition of normal plasma (mixing study) assess for HCV, HIV (from transfusion > 25 years ago)

- Therapy
  - Transfusion as needed for bleeding
  - Factor replacement
    - VIII A
    - IX B
    - Consider prophylactic therapy (↓ arthropathy)

  - Acute bleeding
  - Prophylaxis for minor procedures

  ] Desmopressin

  - IV concentrates of factor VII or IX
  - Desmopressin

SO YOU WANT TO BE A HEMATOLOGIST!

In patient with hemophilia A, diabetes, hypertension, dyslipoproteinemia, and who smokes, and has had a previous TIA, what is the recommended dose of prophylactic aspirin to use?

- Fooled you! Maybe? Correct answer is NO ASA or NSAIDs in hemophilia A or B
- Say it again
- ASA and NSAIDs are contraindicated in patients with hemophilia

THERAPEUTIC CAUTION

- Give the dose of aspirin (ASA) to be used for cardiovascular protection in patient with hemophilia.
  - Ouch! ASA is contraindicated in hemophilia

Acquired Hemophilia

- Definition
  - An acquired reduction in factor VIII from an inhibitor resulting in multifocal mucocutaneous bleeding (not hemarthrosis)
- Associations
  - Postpartum
  - Autoimmune
  - Malignancy
  - Ideopathic (50%)

- Laboratory findings
  - ↓ factor VIII
  - Non–correction on mixing study (i.e. presence of an inhibitor)
- Treatment
  - < 5 Bethesda units factor VIII concentrates
  - > 5 Bethesda units
    - Recombinant human (Rh) VIIa concentrate
    - Prothrombin complex (to activate factor X and intrinsic pathway

Liver Disease and Coagulopathy

- Pathogenesis
  - Coagulopathy
    - ↓ D–dimer clearance
  - Hypo– / –dysfibrinogenemia
    - ↓ fibrinogen
    - ↑ fibrinolysis
  - Thrombocytopenia
    - Hypersplenism
    - ↑ platelet clearance
    - May be refractory to platelet transfusion
- Laboratory
  - ↑ PT
  - ↑ aPTT
  - ↑ TCT
  - ↓ platelets
  - ↓ fibrinogen concentration and function
  - ↑ D–dimer
- Treatment
  - Treat underlying liver disease
  - FFP plus vitamin K

Disseminated Intravascular Coagulation (DIC)

- Pathogenesis
  - Production of normal thrombin leads to:
    - ↑ consumption of clotting factors and platelets
    - ↑ fibrinolysis

- Causes and associations

- Give the causes of DIC.

  - Infection
    - Infection or sepsis (bacterial)
  - Infiltration
    - Malignancies (hematologic and solid organs)
    - Solid tumors
  - Drugs and toxins
    - Snake bite
  - Liver
    - Advanced liver disease
  - Hemolysis
    - Hemolytic transfusion reaction
  - Blood vessels
    - Aortic aneurysm
    - Giant hemangiomas
  - Trauma
    - Massive trauma
    - Burns
  - Obstetrical disorders
    - Abruptio–placenta
    - Amniotic fluid embolism
    - Retained dead fetus

Abbreviations: DIC, disseminated intravascular coagulation

Adapted from: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, page 450.

- Laboratory
  - ↑ PT
  - ↑ aPTT (severe DIC)
  - ↓ fibrinogen } intravascular coagulation
  - ↑ D–dimer }
  - ↓ platelets

- Treatment
  - DIC–associated disorders
    - Obstetrical complications
    - Infection
    - Tissue injury
    - Tumours
      - Solid
      - Leukemia, acute (APL)
    - Bites spider venom
  - Transfusion
    - Plasma
    - Platelets
    - Cryoprecipitate

THERAPEUTIC CHALLENGE

- Give the treatment for pulmonary embolus in patient with cirrhosis and coagulopathy.
  - The coagulation abnormalities which are part of the coagulopathy of the liver disease do not result in "auto–anticoagulation" to the point that it protects them from venous thromboembolism (↑ anticoagulation, but ↑ procoagulant production)
  - Heparin followed by warfarin may be necessary

von Willebrand Disease (vWD)

- Definition
  - Autosomal disorder in which there is ↓ vWF (von Willebrand factor), thereby allowing more factor VIII degradation

- Treatment
  - Treat with desmopressin or vWF–containing factor VIII concentrates

- Why does a woman who suffers from mucocutaneous bleeding and on oral contraceptive pill (OCP) should be considered a case of von Willebrand diseases even if the von Willebrand factor (vWF) is a borderline low?
  - The OCP will increase vWF, as also will exercise, stress, bleeding and inflammation.

- Explain why factor ~ VIIa need to be given to postpartum woman with bleeding and ↑ aPTT, but is not corrected with mixing with normal plasma.
  - ↑ aPTT not corrected with mixing with normal plasma, suggests the presence of an acquired inhibitor of factor VIII developed during pregnancy.
  - Factor rVIIa "….acts to bypass the need for factor VIII by binding to the surface of activated platelets, where it can generate factor Xa, leading to the production of a burst of thrombin and the formation of fibrin" (MKSAP 16, Hematology and Oncology 2012, page 168).

- A woman has severe menorrhagia, and her mother had postpartum hemorrhage. Lab' studies show ↑ aPTT but normal PT. The bleeding time and the Platelet Function Analyzer (PFA-100®) are normal. What is the likely diagnosis and recommended studies to prove the diagnosis?

  - She likely has von Willebrand disease with falsely low levels of vWF.
    - Use of bleeding time, or Platelet Function Analyzer (PFA100®)
    - Bleeding
    - Exercise
    - Inflammation
    - Stress
    - Use of estrogens

- Pathogenesis
    - vWF (von Willebrand factor)
    - Platelets stick to injured vessels
    - Carries factor VIII
- Clinical
    - Primary and secondary failure of homeostasis due to associated ↓ of factor VIII in vWD
- Diagnosis
    - PT normal
    - aPTT – N/↑
    - ↑ bleeding time
    - VIII, N/↓
    - ↓ VWF antigen
    - vWF activity assay
    - Multimer study (for vWD subtypes)

Abbreviation: vWF, von Willebrand factor

- Treatment
    - DDAVP (1–deamino–8–D–arginine vasopressin)
    - VIII concentrate, “intermediate purity”

Abnormal Uterine Bleeding

Interesting stats:

In adolescent women with menorrhagia, ~20% have von Willebrand disease

- Why vWD–associated with VIII–deficiency is not treated with cryoprecipitate?
    - Cryoprecipitate has a greater risk of infusion infection than does intermediate purity of factor VIII concentrate.

TRANSFUSION MEDICINE

- 1 "unit"
  - RBC
    - ↑ hemoglobin 1 g/dL
  - Platelets
    - ↑ platelets 20,000-30,000/mL
  - Iron ~ 250 µg
- FFP
  - Coagulation factors
- Cryoprecipitates
  - VIII, vWF, fibrinogen

- There are many **indications** for RBC transfusions. The interested reader is referred to a general text of their choice in Internal Medicine, or reviews such as UpToDate or MKSAP 16, Hematology and Oncology 2012, Table 19, page 37.

- RBC **targets** for recipients who are actively bleeding

Coronary artery disease (CAD)	Target Hb for transfusion
No	70 g/L (7 g/dL)
Yes	100 g/L (10 g/dL)

Note: In patient who has CAD with possible bleeding from esophageal varices (EV), there is a fine balance for transfusion target.

- Too low
  - May develop cardiac ischemia
- Too high
  - Esophageal varices may rebleed

"Intention is a choice, and Choice is dignity."
Ian Brown

- For the following clinical conditions, give the lower concentration (threshold) at which platelet transfusions should be initiated.

Clinic condition	Threshold for transfusion
➢ Thrombocytopenia, plus	
○ No risk factors	Platelets < 10,000/μL
○ Bleeding into lung, head (cranium)	Platelets < 40,000
➢ Anemia, plus	
○ Most patients	< 7.0 g/dL
○ Acute myocardial infarction	< 10 g/dL

Adapted from: Board Basics 2013, Hematology, Study Table, page 162.

- Give the advantages of performing pre–transfusion leukoreduction.
  - ↓ HLA alloimmunization
  - ↓ non–hemolytic febrile reactions
  - ↓ CMV transmission

- What are the possible sources of preformed alloantibodies in patients receiving blood transfusions?
  - Multiple transfused persons may receive mismatched antigens from previous transfusions
  - Blood from multiparous women as donors

- Give the methods directed to the preparation of blood for transfusion which are intended to prevent 5 types of non–hemolytic transfusion reactions.

Non–hemolytic transfusion reactions	Preparation of blood product
○ Acute lung injury (TRALI)	– Exclude multiparous women as donors
○ Allergic reaction	– Washing of RBCs
○ Anaphylaxis	– Washing of RBCs, or – IgA–deficient donors
○ CMV transmission	– Leukoreduction – CMV–negative donor
○ Febrile reaction	– Leukoreduction
○ GVHD	– Irradiation of RBCs

Abbreviation: CMV, cytomegalovirus; GVHD, graft–versus–host disease; TRALI, transfusion–related acute lung injury

PLASMA PRODUCTS

- To be considered here
  - Fresh frozen plasma (FFP)
  - Cryoprecipitate
- Not to be considered
  - α–AT
  - Anti–thrombin II
  - IV–IG
  - Protein C

Fresh Frozen Plasma (FFP)

➢ Indications

- Give 4 indications for the use of FFP transfusion.
  - TTP
  - DIC
  - Liver disease
  - Warfarin reversal (i.e. intracranial bleeding) +/- PCC
  - Prevention of dilutional coagulation (multiple transfusion of packed RBCs)
  - General factor replacement

➢ Dose

- 10 to 15 mL/kg body weight

Abbreviations: DIC, disseminated intravascular coagulation; PCC, prothrombin complex concentrate (factors II, IX and X); TTP, thrombotic thrombocytopenic purpura

Cryoprecipitate

➢ Indications

- Hypo–/ –dysfibrinogenemia
- Factor VIII deficiency
- Von Willebrand factor
- DIC
- Bleeding from thrombolytic therapy

➢ Dose

- 1 to 2 units per each 10 kg body weight

TRANSFUSION COMPLICATIONS

- Give 6 types of transfusion reactions (not infection or volume overload)
  - Acute hemolysis
  - Delayed hemolysis
  - Post-transfusion thrombocytopenia
  - Non-hemolytic febrile transfusion reaction
    - Donor WBC cytokines
    - Recipient WBC alloantibodies versus donor WBC
  - Allergic reaction
  - GVHD (graft–versus–host disease)
  - TRALI (transfusion–related acute lung injury)

- Give major types of transfusion complications
  - Hemolytic
    - Acute hemolytic transfusion reaction (AHTR)
    - Delayed hemolytic transfusion reaction (DHTR)
  - No-hemolytic
    - Transfusion–associated circulatory overload (TACO)
    - Transfusion–related acute lung injury (TRALI)
    - Febrile non–hemolytic transfusion reaction
  - Allergic reactions and anaphylaxis
  - Transfusion–associated graft–versus–host disease (T–GVHD)
  - Infection

Hemolytic Transfusion Reactions

Acute Hemolytic Transfusion Reaction (AHTR)

- Cause
  - ABO incompatibility between blood donor and recipient, usually arising from a clerical or technical error

- Clinical
  - General
    - Fever
    - Pain at infusion site
  - CVS
    - Hypotension
  - Renal
    - Acute kidney injury (AKI)
  - Blood
    - DIC

Delayed Hemolytic Transfusion Reaction

- Definition: "….an amnestic response to a preformed erythrocyte alloantibody after re–exposure to an erythrocyte antigen outside the HBO system" (MKSAP 16, Hemolytic and Oncology, 2012, page 40).

- Clinical
  - Extravascular hemolysis ~ 1 week after transfusion
  - DHTR in persons with sickle disease → pain crisis

Non–Hemolytic Transfusion Reactions

Transfusion–associated circulatory overload (TACO)

  - Fluid overload causing eart failure (HF) 1 to 2 hours after transfusion
  - Treatment
    - Slow infusion rate
    - Supplement O_2
    - Diuretics

Transfusion–related Acute Lung Injury (TRALI)

- Definition
  - Antibodies in the plasma of the donor are directed against antigens on the neutrophils of the recipient, leading to sequestration in the lungs, damage to the capillaries, and within 6 hours of hemolysis

- Clinical
  - Good prognosis with supportive care
  - Donor should not provide for transfusion

Non–hemolytic Febrile Transfusion Reaction

- Pathogenesis
  - Cytokines from the donor plus leuko–reactive antibodies from the recipient causes an early febrile reaction

- Clinical
  - Stop transfusion
  - Exclude AHTR

- Prevention
  - Give acetaminophen
  - Continue transfusion
  - Pre–transfusion antipyretics
  - Leukoreduction of future transfusion products

Allergic Reactions and Anaphylaxis

- Types
  - Mild
    - Caused by donor plasma proteins
  - Severe
    - Recipients, who are often IgA–deficient, have anti–IgA antibodies which react to donor IgA

- Pathogenesis
  - Donor plasma reacts with IgE on recipient's mast cells

- Treatment
  - Epinephrine, IV fluids
  - Stop transfusion
- Prevention
  - Wash cellular products to remove plasma proteins from blood
  - Use IgA–deficient donors

SO YOU WANT TO BE A HEMATOLOGIST!

A thrombocytopenic patient is transfused with 1 unit of platelets but the platelet count increases only 5000/mL.

- Give the mechanisms of platelet infusion which failed to ↑ platelets > 20,000/mL.
  - ↑ platelet consumption
    - fever
    - sepsis
  - Antibodies developing to platelet antigens

Non–hemolytic Febrile Transfusion Reaction

Pathogenesis	Prevention
WBC – cytokines of donor	– WBC reduction before storage
WBC – recipient allo-antibodies donor WBC	– WBC reduction before storage, or – WBC filtration at bedside (↓ WBC during transfusion)

- Treatment
  - Corticosteroids
  - Acetaminophen or ASA

Transfusion–associated Graft–versus–Host Disease (GVHD)

- Definition
  - Donor lymphocytes become engrafted in an immune compromised recipient, causing damage to skin, GI mucosa, and pancytopenia

- Pathogenesis
  - Lymphocytes of donor engraft in an immunocompromised recipient
- Persons at risk
  - Premature infants
  - Chemotherapy patients
  - 1st degree relative of donor
- Clinical
  - Donor lymphocyte damage to the:
    - Skin
    - Bone marrow
    - Liver
    - GI tract
- Prevention
  - Gamma irradiation of cellular blood components in at–risk population
- Prognosis
  - Often fatal
- Treatment
  - Supportive only
    - No proven effective treatment

Infection

Viral infections	Risk per million (10^6)
HIV	0.5
HCV	1
HBV	< 30

- Other infections of concerns
  - West Nile virus (WNV)
  - Creutzfeldt–Jakob disease (CJD)
  - Chagas disease
  - Babesiosis

- Give the name of the bacterial organism which may cause fatal sepsis from a platelet transfusion.

  - *Yersinia enterocolitica* from platelets stored at room temperature

Therapeutic Apheresis

- Definition
  - "….the separation of whole blood into its components, treatment or removal of the affected components and return of the remaining blood products" (MKSAP 12, Hematology and Oncology, 2012, page 41).
  - Plasmapheresis
    - Removal of patient plasma with replacement of donor plasma (plasma exchange or an albumin or saline mixture"

CLINICAL CAUTION

Beware of the development of hypocalcemia in patients treated with therapeutic apheresis.

- Give indications for therapeutic apheresis (standard first–line, or supportive adjuvant therapy)

System	Primary	Adjuvant
○ CNS and PNS	– Acute or chronic demyelinating polyneuropathy – Myasthenia gravis – IgM–related polyneuropathy	▪ Lambert–Eaton syndrome ▪ Acute CNS MS
○ Blood	– Cryoglobulinemia TTP – Sickle cell disease with end–organ complications – Acute leukemia with leukocytosis	▪ Thrombocytosis with symptoms
○ Kidney	– Goodpasteur syndrome – GP (WG)–related RPGN – Renal transplant rejection, antibody mediated	▪ Myeloma cast nephropathy
○ Endocrine		
○ Metabolic	– Familial homozygous – Hypercholesterolemia	
○ Infection		▪ Severe malaria
○ CVS		▪ Cardiac transplantation rejection

Abbreviations: CNS, central nervous system; GP, granulomatosis with polyangiitis; MS, multiple sclerosis; PNS, peripheral nervous system; RPGN, rapidly progressive glomerulonephritis; WG, Wegener's granulomatosis

Adapted from: MKSAP 16, Hematology and Oncology, 2012, Table 21, page 41.

CLINICAL ALERT

In patient treated with systemic hypertension, give the class of medications that must be stopped 24 hours before elective therapeutic apheresis.

FEBRILE NEUTROPENIA

In a patient with leukemia and antibiotic treatment who develop febrile neutropenia, suspect angio–invasive aspergillosis. If chest X–ray shows infiltration, perform CT of the chest.

- Give the CT of the chest findings in patients with invasive aspergillosis.
    - Infiltrates
        - Nodular
        - Patchy
        - Ground–glass, “halo” sign

➢ Treatment
- Start with anti–pseudomonas
    - Meropenem
    - Imipenem
    - Cefepime
    - Pip–tazo (piperacillin–tazobactam)
- If poor response, add
    - Aminoglycoside
    - Fluoroquinolone +/-
    - Vancomycin
- Do **not** use
    - Colony–stimulating factors for neutropenia
    - Anti–viral therapy, unless there is evidence of viral infection

PLASMA CELL DYSCRASIAS

➢ Definition
- “….abnormal clonal proliferation of immunoglobulin–secreting differentiated B–lymphoid cells and plasma cells”
- A malignancy of plasma cells involving the bone and bone marrow (≥ 10% clonal plasma cells)
- ↑ production of monoclonal (M) protein (≥ 3 g/dL)
    - ↑ heavy chain IgG, IgA or IgD, +/-
    - ↑ light chain κ, λ
    - Non–secretory disease is rare
- End–organ damage

Source: Board Basics 2013, Hematology, page 163.

- Types
  - Multiple myeloma
  - Monoclonal gammopathy of undetermined significance (MGUS)
  - Waldenström's macroglobulinemia
  - AL amyloidosis (light–chain–associated amyloidosis)
- Clinical
  - Bone
    - Vertebral compression fractures
    - Osteopenia or osteoporosis
    - Lytic bone lesions
    - Hypercalcemia
  - Blood anemia
  - Kidney disease
  - Bone pain from lytic lesions
  - Spinal cord compression
  - Blood
    - Anemia
    - Leukopenia
    - Thrombocytopenia
  - Lab: ↑ serum
    - Creatinine
    - Calcium
    - M protein (97%)

- Give common renal abnormalities in multiple myeloma.
  - ↓ serum creatinine
  - Cast nephropathy
  - AL amyloidosis
  - Albuminuria
  - M protein
  - Treatment related
    - Focal segmental glomerulosclerosis (FSG) from pamidronate for prevention of pathological fractures
    - Acute tubular necrosis (ATN) from zoledronic acid (bisphosphonate)

CLINICAL ALERT

About half of patients with multiple myeloma have renal injury, which can be worsened by nephrotoxic drugs such as NSAIDs.

- Diagnosis
  - Serum, urine
    - ↑ monoclonal M protein
  - Bone marrow
    - ↑ clonal plasma cells
    - Plasmacytoma
  - MGUS
    - ↑ serum monoclonal protein, but < 3 gm
    - Bone marrow ↑ clonal plasma cells, but < 10%
    - No end–organ damage in bone, blood, kidney
  - AL amyloidosis
    - Serum and urine light–chains
    - May also affect tongue, liver, heart

- Spectrum: important factors
  - M protein in the serum
  - % bone marrow plasma cells
  - B2 microglobulin (serum)
  - End-stage damage
    - Serum Ca^{2+}> 2.6 mmol/L (> 10.5 mg/dL)
    - Serum creatinine > 1777 µmol/L (> 2 mg/dL)
    - Hemoglobin
      - < 100 g/L (< 10 g/dL), or
      - 20 g/L < LLN (2 g/dL < LLN)
    - Bone disease
    - Hyperviscosity syndrome
    - AL amyloidosis
    - Recurrent bacterial infections

Diagnosis of dyscrasis	M protein > 3 g/dL	Bone marrow plasma cells ≥ 10, %	MROD	S B2-microglobulilin
MGUS	-	-	-	-
↓ 1% per year				
Myeloma				
Asymptomatic*	+	+	-	-
↓				
Symptomatic	+	+	+	Stage I* > 3.5 mg/L II in between III > 5.5 mg/L

*May have M protein ≥ 3 g/dL and/or ≥ 10% bone marrow plasma cells
* in stage I, serum albumin ≥ 35 g/L (3.5 g/dL)

Abbreviations: MGUS, monoclonal gammopathy of undetermined significance

- Give the risk factors for the progression of asymptomatic to symptomatic multiple myeloma (MM).
  - M protein concentration
  - % of plasma cells in bone marrow
  - ↑ free light chains
  - ↓ non–clonal light chains

  } ↓ serum K^+ / free light chains

➢ Treatment
  - Pharmaceutical
    - Melphalan
      - Alkylating agent
    - Corticosteroids
    - Thalidomide, or Lenalidomide
      - Immunomodulatory
    - Bortezomib
      - Protease inhibitor

- Hematopoietic stem cell transplantation (HSCT)
  - Induction
    - Dexamethasone, bortezomib +/-
    - Thalidomide or lenalidomide
  - Consolidation
    - Melphalan
  - Relapses

    Bortezomib or lenalidomide

- Therapy (of multiple myeloma)
  - Indication
    - Symptoms
  - < 75 years
    - Human stem cell transplantation (HSCT)
    - Vigorous pretransplant induction chemotherapy
      - Dexamethasone plus lenalidomide or thalidomide
      - Bortezomib, used alone for induction or relapse
  - > 75 years
    - Prednisone plus melphalan (do **not** use for HSCT induction therapy)

  - Care of complications
    - Bone
      - Spinal cord compression
    - Corticosteroids
    - Radiation
      - Pathological fractures
      - Osteoporosis
    - Blood
      - Hyperviscosity syndrome
    - Plasmapheresis
      - Anemia
    - Erythropoietin
    - Infections and Immunization
      - Pneumococcus
      - Influenza
      - Immunoglobulin (for frequent bacterial infections)
      - Varicella–zoster vaccine (uses to rescue bortezomib)

- In patient with multiple myeloma, give the symptoms suggesting hyperviscosity syndrome, and the need for plasmapheresis.
    - Eyes
        - Blurred vision
    - CNS
        - Altered mentation
        - Headaches
        - Fatigue
    - Heart
        - Heart failure (HF)
    - GI
        - Mucosal bleeding

MELANOMA

- Common risk factors
    - Sunshine, especially
        - In childhood
        - Fair skin
        - Repeated sunburns
    - Cutaneous nevi
    - Family history
    - BRAF gene V600E mutation

- Treatment
    - Surgical excision
        - < 1 mm
        - No ulceration
        - Low intake index
    - Sentinel lymph node biopsy (SLNB)
        - Positive–regional lymph node dissection
    - Follow–up for annual skin examinations
    - Metastatic disease
        - IV dacarbazine
        - po temozolomide
        - Ipilimumab
        - Vemurafenib (for patients who have BRAF gene V600E mutation)

- Give the reason why melphalan is used for non–HSCT treatment of MM, and for consolidation therapy for human stem cell transplantation (HSCT), but not for induction.

    - Melphalan is toxic to stem cells, so is not used initially after HSCT
    - Complications
        - Lytic bone disease
            - Kyphoplasty, for spinal stability
            - Radiation, for palliation of pain
            - Bisphosphonates, for prevention of pathological fractures
        - Renal failure
            - Treat ↑ serum Ca^{2+}
            - Avoid nephrotoxins
            - Plasmapheresis
        - Cast nephropathy
        - Free light chains
        - Chemotherapy, for ↑ light chains

- Give the risk of treating multiple myeloma (MM) with high dose dexamethasone with lenalidomide.

    - High risk of venous thromboembolism (VTE), approximately 8 – 16% for relapsing MM, even higher for new diagnosis of MM.

- Give the differences between multiple myeloma and multiple myeloma syndromes.

    - Multiple myeloma
        - ≥ 10% clonal plasma cells on bone marrow biopsy

    - Multiple myeloma syndrome
        - Multiple myeloma **plus** end–organ damage

MYELOPROLIFERATIVE DISORDERS

- Definition: "….a group of clonal cell disorders characterized by absent regulation of proliferation that results in excess production of myeloid elements in the bone marrow"

Source: Board Basics 2013, Hematology, page 164

➢ Types	○ WBC	Chronic myeloid leukemia (CML)
	○ Platelets	Essential thrombocythemia
	○ RBC	Polycythemia vera
	○ Fibroblasts	Myelofibrosis

Chronic Myeloid Leukemia (CML)

- Definition: "….a hematopoietic stem cell disorder characterized by myeloid proliferation associated with (9; 22) (q 34: q 11) translocation, the Philadelphia chromosome.

- Clinical
  - CML may undergo
    - Accelerated phase (blasts cells are 10%-20% of leucocytes)
    - Blast crisis (blast cells are > 20% of leucocytes)

  - Transformation into
    - Acute leukemia
      - Myeloid
      - Lymphoid

- Diagnosis
  - Cytogenic study of bone marrow – Philadelphia chromosome
  - Bcr–abl gene

- Treatment
  - Often no treatment required
  - Young, accelerated phase or blast crisis
    - HSCT

- Disease control or molecular remission
  - Imatinib mesylate
  - Dasatinib
  - Nilotinib
- Palliation hydroxyurea
- Platelet transfusion
  - Bleeding < 10,000/mL
- Splenectomy
  - Painful splenomegaly
  - Multiple transfusion requirements
  - Despite imatinib mesylate or hydroxyurea

Conventional cytogenic testing may miss subtle changes which would elute the diagnosis of chronic myeloid leukemia (CML).

- Give the value of fluorescence in situ hybridization (FISH) to diagnose CML.
  - FISH testing of the peripheral blood is sensitive to detect (9;22) translocations

- Give the limitation of flow cytometry of peripheral blood to diagnose CML.
  - Flow cytometry is limited in its role to diagnose CML because the CML cells:
    - Do not have varying stages of myelopoiesis
    - Do not express aberrant cell surface

Essential Thrombocythemia

- Definition
  - Platelet count > 600 x 10^9/L (600,000 µL) on 2 different occasions separated by at least 1 month in patient with no other cause of thrombocythemia

- Pathogenesis
  - Myeloproliferative disorder characterized by:
    - Platelets > 600,000 mL
    - ↑ Bone marrow megakaryocytes
    - Clinical complications of
      - Thrombosis
      - Hemorrhage
  - Associated with JAK2 mutation (in 50%)

- Give the mechanism of bleeding disorders in essential thrombocythemia.
  - ↑↑ platelets
    - Qualitative dysfunction similar to vWD

- Clinical
  - ~ ½ have mutation in JAK2
  - Hepatomegaly, ~20%
  - CNS
    - Headaches
    - Visual disturbance
    - TIA and CVA
  - Skin
    - Erythromelalgia (red, warm, swollen, painful hands or feet)
    - Livedo reticularis
  - Splenomegaly (in 50%)
  - CVS
    - Coronary obstruction or ischemia (CAD) / myocardial infarction (MI)
  - GI
    - Bleeding

- Laboratory
  - Peripheral blood
    - Megakaryocytes
    - Leucocytosis
    - Basophilia
  - Bone marrow
    - Hypercellular
    - Hyperplasia of megakaryocytes
    - Clusters of megakaryocytes

- Treatment
  - No symptoms
    - ASA 81 mg *po OD*
    - Follow–up
  - Erythromelalgia
    - ASA 81 mg *po OD*
  - Mild symptoms
    - ASA 81 mg *po OD*, plus
    - Hydroxyurea, anagrelide, or interferon alpha (IFN–α)
  - Severe
    - CNS, CVS, GI symptoms:
      - Hydroxyurea plus platelet
      - Apheresis

Polycythemia vera (PV)

- Clinical (thrombosis and bleeding)
  - ↑↑↑ RBC mass ↑ hematocrit
    - M > 60%
    - W > 56%
  - ↑ WBC and platelet
  - JAK2 V617F mutation (in 95%)
  - ↓ erythropoietin
  - Splenomegaly
  - ↑ cellularity in bone marrow
- Clinical
  - CNS
    - Headaches
    - TIA or CVA
  - CVS
    - MI
    - DVT
  - GI
    - Budd–Chiari syndrome (BCS)
  - Skin
    - Facial plethora
    - Erythromelalgia
    - ↑ pruritis with hot water

- Therapy
  - Phlebotomy
    - Lower hematocrit
      - M > 60% → < 45%
      - F > 56% → < 42%
  - Hydroxyurea
    - > 60 years
    - Previous thrombosis
  - ASA 81 mg *po OD*
  - Allopurinol for hyperuricemia
  - Anti–histamines
    - Pruritis

- Give the reason why low–dose rather than standard– / –high dose ASA is given for polycythemia vera (PV) or for essential thrombocythemia (ET).
  - PV and ET are associated with thrombosis and bleeding
  - Low–dose ASA will ↓ risk of thrombosis, but high–dose ASA would ↑ risk of bleeding (while ↓ risk of thrombosis)

- Give the diagnostic features of polycythemia vera.
  - Hemoglobin (Hb) concentration, g/L:
    - Women 165 (16.5)
    - Men 185 (18.5)
  - Leukocytosis
  - Thrombocytosis
  - Hepatosplenomegaly
  - Mutation JAK1 VG17F

BUZZ WORDS

- Itchy skin after bath (!)
- Philadelphia chromosome (BCR–ABL)
- Craving for ice cubes (!)
- ↑ aPTT failing to correct with normal plasma (“mixing test”)
- Polycythemia vera
- Chronic myeloid leukemia (CML)
- Iron deficiency (!)
- Acquired hemophilia (acquired antibody to factor VIII)

- Give the role of measuring blood erythropoietin concentration in patients with polycythemia (erythrocytosis).

Types of polycythemia	Erythropoietin lever
Primary	↓
Secondary	↑

Myelofibrosis with Myeloid Metaplasia (MMM)

- Pathogenesis
  - Clonal proliferation of abnormal hematopoietic stem cells in the bone marrow release cytokines which ↑ production of fibroblasts
  - ↑ fibroblasts fibrosis of marrow, and marrow failure

SO YOU WANT TO BE A HEMATOLOGIST!

- Describe the peripheral blood smear of a patient with myelofibrosis with myeloid metaplasia (MMM).
  - RBC
    - Tear drop
    - Nucleated
    - Erythroblasts
  - Platelets
    - Giant

- Clinical
  - Bone marrow failure → extramedullary hematopoiesis → splenomegaly or hepatomegaly → PHT (portal hypertension)
  - MMM may transform to acute leukemia
  - < 60 years
    - HSCT
  - > 60 years
    - Supportive therapy

Bony Sclerosis

Sclerotic lesions may be seen in the skull of patients with myelofibrosis

- Give a systematic approach to the causes of sclerosis (increase in bone density).

    - Long bones
        - Paget's disease
        - Metastases
            - Prostate
            - Breast
            - Reticuloses
            - Usually in spine, pelvis, ribs
            - May grow outside the bone, unlike Paget's disease
        - Chronic osteomyelitis
        - Myelofibrosis
        - Avascular necrosis
        - Marble bone disease (osteopetrosis)
        - Fluorosis
    - Skull
        - Meningioma hyperostosis frontalis

Adapted from: Davies, I.J.T. *Lloyd-Luke (medical books) LTD* 1972, page 221.

Trick and Red Herrings

- Why splenectomy is not performed in patients with myelofibrosis with myeloid metaplasia (MMM)?
    - No survival benefit
    - ↑ risk of:
        - Transformation of MMM to leukemia
        - Hemorrhage
        - Thrombosis

CHRONIC MYELOID DISORDERS

SO YOU WANT TO BE A HEMATOLOGIST!

- Give the "chronic myeloid disorders".
  - Chronic myeloid leukemia
  - Myelodysplastic syndrome
  - Atypical chronic myeloid disorder
  - Chronic myeloproliferative disease
    - Polycythemia vera
    - Myelofibrosis with myeloid metaplasia
    - Essential thrombocythemia
    - Agnogenic myeloid metaplasia
    - Post–polycythemic myeloid metaplasia
    - Post–thrombocythemic myeloid metaplasia

Source: Baliga, R.R. *Saunders/Elsevier* 2007, page 317.

Myelodysplastic Syndromes (MDS)

- Presentation
  - Refractory anemia plus, ↑ blasts–2
  - Unilineage (or multi–lineage) dysplasia
- Cause
  - Malignant clonal abnormalities usually affecting chromosomes 3, 5, 7, 8 and 17
  - These clonal abnormalities result in:
    - Cytopenia in ≥ 2 of 3 call lines (RBC)
      - ↑ MCV
      - Nucleated
      - Teardrop
- Clinical course
  - Worsening anemia leukopenia, thrombocytopenia
  - Transformation to acute leukemia
  - Bone marrow failure
- Differential
  - Deficiency of folate and cobalamin
    - Alcohol
    - Drugs
    - Myeloproliferative disorders

- Therapy
  - Asymptomatic
    - Follow–up
  - Symptoms
    - Erythropoietin
    - Granulocyte colony–stimulating factor (GCSF)
    - HSCT
  - 5q subgroup of MDS
    - Lenalidomide

- A higher risk myelodysplastic syndrome (MDS) is diagnosed. Give the recommended therapy for newly diagnosed MDS.
  - Azacitidine

SO YOU WANT TO BE A HEMATOLOGIST!

- Give the difference between “myeloid metaplasia” and “extramedullary hematopoiesis”?
  - None; both represent ectopic hematopoietic activity, usually in the liver and spleen, and may not be associated with myelofibrosis (bone marrow fibrosis).
- Give the meaning of “myelofibrosis with myeloid metaplasia” (MMM).
  - By convention, MMM is an idiopathic myelofibrosis.

Hematopoietic Growth Factors

- Indications for use
  - Erythropoiesis–stimulating agents (ESA, i.e. epoetin, darbepoetin alfa)
    - Cancer–related symptomatic anemia (hemoglobin ≤ 100 g/L [≤ 10 g/dL) when chemotherapy is not curative
    - Chronic renal failure +/- hemodialysis when hemoglobin < 100 g/L
    - Serum iron saturation should be ≥ 20%, and serum failure 100 – 200 µg/mL (100 – 200 ng/mL)

- Granulocyte–macropahge colony–stimulating factor (G–CSF and GM–CSF)
  - Primary prophylaxis for neutropenia in patients undergoing myelosuppression
  - Patients with non–malignant disease who have infection–associated neutropenia
- Thrombopoietin
  - Relapsing idiopathic thrombocytopenic purpura (ITP)

Chemotherapy–Induced Myelodysplastic Syndrome

- Definition
  - Myelodysplastic syndromes are stem cell disorders causing hypercellular bone marrow dyserythropoiesis, which in turn causes ineffective hematopoiesis and peripheral cytopenias, with onset at months to years after chemo– or radiotherapy

- Diagnosis
  - Bone marrow cytogenetic studies show chromosomal changes, without lymphadenopathy or hepatosplenomegaly

EPSTEIN–BARR VIRUS (EBV) **INFECTION**

- Clinical

Although EBV infection is usually associated with infectious mononucleosis syndrome (IMS) (flu–like illness, fever, posterior cervical lymphoadenopathy, asplenomegaly, sore throat, measles–like rash after ampicillin, atypical peripheral blood lymphocytes and positive serology), some patients may have atypical presentations.

- Give the other presentations of EBV infection other than the typical IMS or EBV–associated malignancies.

o CNS	– Aseptic meningitis – Aseptic encephalitis
o Liver	– Hepatitis
o Blood	– Hemolytic anemia – Thrombocytopenia

- Name 3 viruses which are associated with infectious mononucleosis syndrome (IMS)
    - EBV
    - CMV
    - HIV

➢ Complications

- Give malignant or premalignant conditions associated with EBV.
    - Lymphoma
        - B–cell lymphoma
        - T–cell lymphoma
        - Hodgkin's lymphoma
        - Post–transplantation lymphoproliferative disorder (PTLD)
    - Leukoplakia, Or
        - Painless, white, corrugated plaques on the edge of the tongue
    - Nasopharyngeal carcinoma
    - Hodgkin's lymphoma may be due to Epstein–barr Virus (EBV)
    - An entire lymph node must be examined histologically to differentiate from non–Hodgkin's lymphoma, i.e.:
        - Burkitt's lymphoma
        - Diffuse large B–cell lymphoma

Beware the "company" that diseases keep.

- In a patient with oral hairy leukoplakia, in addition to EBV infection, give the other viral infection which must be excluded.
    - Oral hairy leukoplakia is highly suggestive of an infection with HIV

➢ Diagnosis

- Give the serological tests for the present and past EBV infection.

	EBV Infection	
	Present acute primary	Past
○ Viral capsid antigen IgM	↑	0
○ Early antigen IgE	↑	0
○ Epstein–barr nuclear antigen–1 IgE	↓ / 0	↑

Note; VCA (viral capsid antigen) IgG is increased in both, thus does not help to distinguish between present and past EBV infection

➢ Treatment
  - ○ Conservative
  - ○ No anti-viral drugs
  - ○ Corticosteroids for severe
    - Lung disease
    - Hemolytic anemia

LYMPHADENOPATHY AND MASS IN HEAD, NECK AND AXILLA

For a list of the common sites and characteristics of lymphadenopathy, please see: Filate, W., *et al*. Essentials of Clinical Examination Handbook. 5th Edition. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, pages 120 and 121.

➢ Clinical: Generalized Lymph Node Enlargement
  - ○ Examine the mouth for the following signs:
    - Tonsillar lymph nodes
    - Palatal petechiae and pharyngitis (glandular fever)
    - Neoplastic tumors and ulcers
  - ○ Examine other lymph node areas in a systemic manner: submental, submadibular, deep cervical (upper and lower), occipital, posterior triangle, supraclavicular, axillary, epitrochlear and inguinal
  - ○ Upper cervical lymph nodes: examine the chest, breast and upper limbs. Also, perform an ear, nose and throat (ENT) examination for nasopharyngeal carcinoma
  - ○ Lower cervical and supraclavicular lymph nodes: examine the thyroid, chest, abdomen for gastric carcinoma (Virchow's nodes) and testis
  - ○ Axillary lymph nodes: examine the chest, breast and upper limbs
  - ○ Inguinal lymph nodes: examine the lower limbs and external genitalia

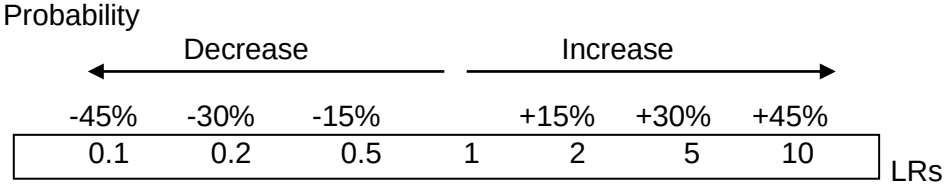
For the differential diagnosis of neck mass, please see: Filate, W., *et al*. Essentials of Clinical Examination Handbook. 5th Edition. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, page 106.

- Give the performance characteristics for lymphadenopathy.

Findings	PLR	NLR
➢ General		
○ Age ≥ 40 years	2.4	0.4
○ Weight loss	3.4	0.8
➢ Distribution of Adenopathy		
○ Supraclavicular nodes	3.2	0.8
➢ Characteristics of Adenopathy		
○ Lymph node size		
– ≥ 9 cm^2	8.4	
○ Hard texture	3.2	0.6
○ Fixed lymph nodes	10.9	NS
➢ Lymph Node Score		
○ 5 or 6	5.1	
○ 7 or more	21.9	

Abbreviation: NLR, negative likelihood ratio; PLR, positive likelihood ration.

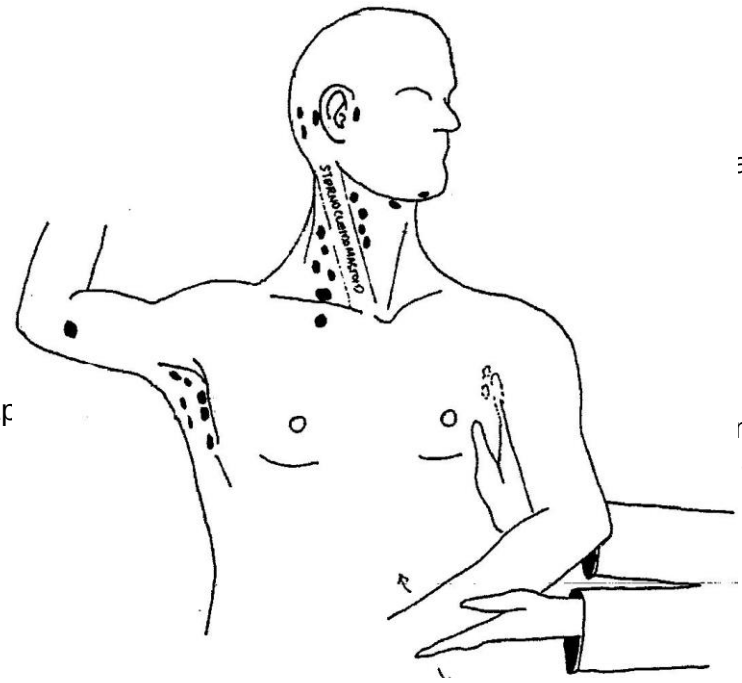
Note that there a number of findings which are not listed here, because their PLR is < 2. These include male sex, fever, head and neck nodes (excluding supraclavicular nodes), axillary nodes, inguinal nodes, epitrochear nodes, generalized lymphadenopathy, lymph node size < 4 cm or 4 – 8.99 cm^2, lymph node tenderness, rash, palpable spleen, palpable liver, lymph node score ≤ 4.



Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 24.1, page 292.

Clinical pearl: *90% of pediatric neck masses are inflammatory, whereas 90% of adult neck masses are metastatic.*

- Lymph nodes of the head, neck and axilla



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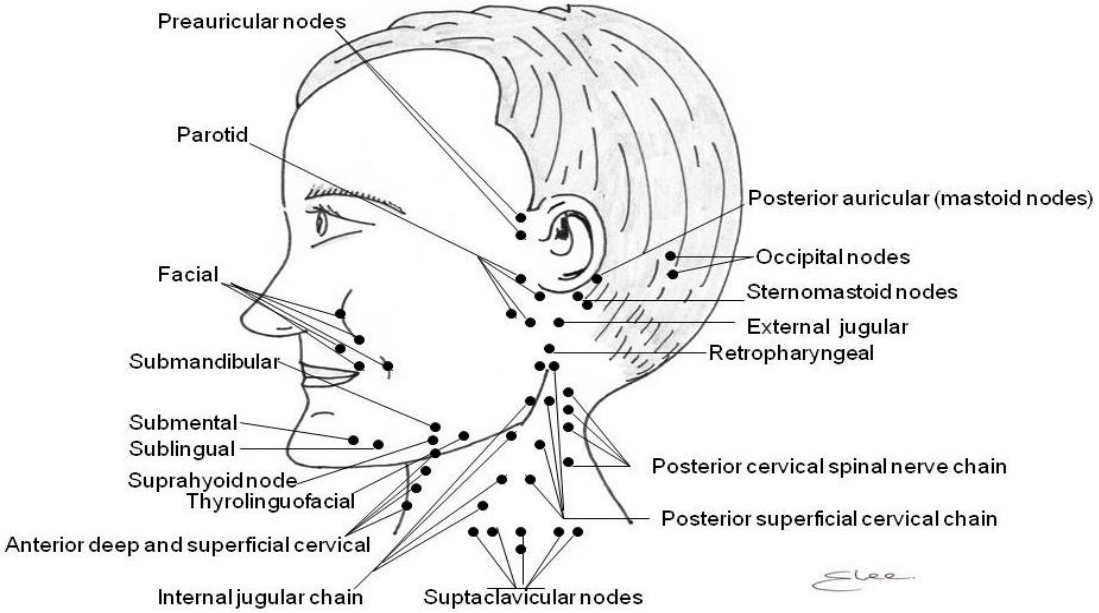
Useful background: Perform a focused examination for cervical lymphadenopathy



Adapted from: Mangione, S. *Hanley & Belfus* 2000, page 401

SO YOU WANT TO BE A HEMATOLOGIST!

- Give the types and causes of regional lymphadenopathy.
  - Cervical lymphadenopathy
    - Infectious
      - Bacterial pharyngitis
      - Dental abscess
      - Otitis media
      - Infectious mononucleosis
      - Cytomegalovirus
      - Gonococcal pharyngitis
      - Toxoplasmosis
      - Hepatitis
      - Adenovirus
    - Malignancies
      - Non–Hodgkin's disease
      - Hodgkin's disease
      - Squamous cell carcinoma of the head & neck
  - Virchow's node (anterior left supraclavicular lymph node) or Troisier's ganglion
    - Carcinoma of the breast, bronchus, lymphomas and gastrointestinal neoplasms
  - Delphian node (a midline prelaryngeal lymph node)
    - Laryngeal malignancy
    - Heralds thyroid disease
    - Lymphoma
  - Axillary lymphadenopathy
    - Infectious
      - Staphylococcal
      - Streptococcal infections of the arm
      - Cat scratch fever
      - Tularaemia
      - Sporotrichosis
    - Malignant
      - Hodgkin's disease
      - Non–Hodgkin's lymphoma
      - Carcinoma of breast and melanoma
  - Epitrochlear lymphadenopathy
    - Most common causes are lymphoma or CLL and infectious mononucleosis
    - Other diagnoses include HIV, sarcoidosis, and connective tissue disorders
    - In developing countries secondary syphilis, lepromatous leprosy, leishmaniasis and rubella are important causes

Printed with permission: Baliga, R.R. *Saunders/Elsevier* 2007, pages 570 and 571.

- What lymph node area, source of drainage, and causes of common lymphadenopathy?

Lymph node areas	Areas of drainage
➢ Head and neck	
o Pre–/ postauricular	- Eye, scalp
o Occipital	- Posterior scalp
o Submental	- Lower face, floor of mouth
o Submandibular	- Face, oral cavity
o Cervical	
o Anterior	- Pharynx, tonsils, face, scalp
o Posterior	- Posterior scalp, ear
➢ Clavicular and axillary	
o Clavicular - Supra–/ infraclavicular	- Cervical lymph node chains, abdomen, thorax, arm and breast
o Axillary	- Other axillary nodes
- Central	
- Lateral	- Most of arm
- Posterior (subscapular)	- Posterior chest wall, upper arm
- Anterior (pectoral)	- Anterior chest wall, most of breast
➢ Upper Extremities	
o Superior to the clavicle	- Head, neck & axillary nodes
o Posterior to the clavicle	- Head, neck & axillary nodes
o At apex of axilla	- All other axillary nodes
o High in axilla, deep to pectoralis minor	- Pectoral, subscapular and lateral nodes
o Along lower border of pectoralis major, inside anterior axillary fold	- Anterior chest wall, most of breast
o Along lateral border of scapula, deep in posterior axillary fold	- Anterior chest wall, most of breast
o Upper humerus	- Most of arm
o Epitrochlear (cubita)	- Lower arm
o Above medial epicondyle	- Ulnar side of hand & forearm

Lymph node areas	Areas of drainage
➢ Lower extremities	
o Upper portion of the legs	- Superficial tissue of upper portion of the leg
o Below inguinal ligament	- Skin of: ▪ lower abdominal wall ▪ external genitalia (not testes) ▪ lower 1/3 of vagina ▪ gluteal area
o Medial aspect of femoral vein	- Popliteal node and superficial inguinal nodes
o Popliteal fossa	- Heel and outer aspect of foot
o Epitrochlear	

Adapted from: Filate, W., *et al*. *The Medical Society, Faculty of Medicine, University of Toronto*, 2005, pages 116-120; and Baliga, R.R. *Saunders/Elsevier* 2007, page 570; McGee, S.R. *Saunders/Elsevier* 2007, pages 116 and 117.

Neck and Axillary Lymphadenopathy

➢ Clinical

- Take a directed history and perform a focused physical examination for mass or lymph nodes in the neck and axilla.

  - o General considerations
    - Lymph nodes found in normal individuals are small, mobile discrete, non–tender
    - Enlargement of a supraclavicular node suggests possible metastasis from a thoracic or an abdominal malignancy, especially on the left supraclavicular node
    - Tender nodes suggest inflammation; hard or fixed nodes suggest malignancy
    - Lymph nodes should be movable in two directions: up and down, and side–to–side (neither a muscle nor an artery).

- Description
  - Location and if localized or generalized
  - Size
  - Shape
  - Consistency (hardness of node is neither sensitive nor specific of malignancy)
  - Tenderness
  - Mobility
  - Confluence or matting with other nodes
  - Dimpling or drainage to overlying skin

Use the mnemonic **ALL AGES** to approach a patient with lymphadenopathy

- **A**ge at presentation (i.e. infectious mononucleosis is common in younger age groups; Hodgkin's disease has a bimodal peak)
- **L**ocation(s) of lymph nodes (lymph nodes present outside the inguinal regions and for longer than one month and measuring 1 cm x 1 cm or larger without an obvious diagnosis should be considered for biopsy)
- **L**ength of time the lymph nodes are present
- **A**ssociated symptoms and signs including fever ("B" symptoms: temp > 38°C, drenching night sweats, unexplained weight loss > 10% body weight)
- **G**eneralized lymph node enlargement
- **E**xtranodal organ involvement
- **S**plenomegaly (rare in metastatic cancer; consider infectious mononucleosis lymphoma, chronic lymphocytic leukemia, and acute leukemia)

Source: McGee SR. *Saunders/Elsevier* 2007, page 569.

- History
  - Onset of symptoms, duration, alleviating or aggravating factors, other associated symptoms, progression of symptoms
  - Unilateral or bilateral
  - Delimitation (borders)
  - Epistaxis and nasal obstruction
  - Oral pain
  - Otalgia (referred)
  - Dysphagia, hoarseness, stridor
  - Environmental or occupational exposures (i.e. radiation, asbestos)
  - Travel history
  - HIV, EBV, TB
  - Symptoms of thyroid dysfunction

- Medications (i.e. phenytoin, allopurinol)
- Exposure to animals
- History of cancer
- IV drug use
- Cardiac problems, review of systems

➢ Physical examination

- Perform a directed physical examination for lymph nodes in the neck and axilla.
  - Occipital lymph nodes
    - Located at the junction between head and neck, common in childhood infections
    - In adults, a sign of scalp infection
    - In the absence of infection, usually reflect a generalized lymphadenopathy, i.e. HIV infection
  - Posterior cervical lymphadenopathy
    - Dandruff or nasopharyngeal tumor
  - Pre–auricular nodes
    - Lymphoma or on the same side of conjunctivitis (often referred to as Parinaud's syndrome)
  - Nodes scattered around the two branches of the mandible
    - Localized pathology, i.e. periodontitis or other teeth infection
    - Submental and submandibular nodes reflect cancer of the nose, lip, anterior tongue, or anterior floor of the mouth
  - Mid–jugular nodes
    - Cancer of the base of the tongue or larynx
  - Lower jugular nodes
    - Primary cancer of the thyroid or cervical esophagus
  - Non–nodal findings
    - Myositis, torticollis
    - Salivary gland
      - Calculi
      - Thyroid, thyroglossal duct cyst*, thyroid tumor, goiter, or pyramidal lobe

Adapted from: Mangione, S. *Hanley & Belfus* 2000, pages 400-1; Talley, N.J., *et al*. *Maclennan & Petty Pty Limited*, 2003, page 233, 235; McGee, S.R. *Saunders/Elsevier* 2007, pages 284-90; Filate, W., *et al*. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 119-21; and Davey, P. *Wiley-Blackwell* 2006, pages 82 and 83 and Baliga, R.R. *Saunders/Elsevier* 2007, pages 570-1.

ANEMIA

➢ Clinical

- Take a directed history for anemia.

- History

  - Fatigue
    - Duration
    - Onset
    - Course
    - Frequency
    - Limitations in activities

  - Associated symptoms
    - Malaise
    - Weakness
    - Dyspnea
    - Chest pain
    - Palpitations
    - Headache
    - Tinnitus
    - Presyncope and syncope
    - Craving for ice

  - Potential sites of blood loss
    - Previous past anemia
    - Menstrual bleeding (changes in frequency, amount, duration of menses)
    - Respiratory. tract hemoptysis, epistaxis
    - GI bleeding melena, hematochezia, hematemesis
    - Urinary or renal bleeding (hematuria)
    - Previous multiple blood donations (frequency, last donation, amount donated)

  - Dietary history
    - Iron deficiency
    - Folic acid or B12 deficiency
    - Alcohol
    - Vegans

- Past medical history
  - Chronic inflammatory disorders
  - Liver or renal disease
  - Endocrine disorders (hypo–/ hyperthyroid, Addison's disease)
  - Malignancies (myeloma, leukemia)
  - Alcohol use (quantity, duration)
  - Lead exposure
  - Medications (ASA, NSAIDs, chemotherapeutic agents)

- Family medical history
  - Genetic background (Mediterranean/ African/ Asian)
  - Hereditary anemia (sideroblastosis, spherocytosis, elliptocytosis, stomatocytosis)

- Perform a focused physical examination for anemia.

○ Eyes	- Palor
○ Mouth	- Glossitis
○ Thyroid	- Goiter
○ Hands	- Pallor
	- Lose of palmar crease
○ Heart	- Heart failure (HF)
	- Atrial myxoma
○ Lung	- Bronchiectasis
	- Abscess
	- Cancer
○ Liver	- Cirrhosis
○ Spleen	- Splenomegaly
○ Nodes	- Lymphadenopathy
○ MSK	- Rheumatoid arthritis
	- Lupus
○ Malnutrition	- Muscle wasting
	- Palor
	- Edema

Adapted from: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, pages 15 and 16.

- Give the performance characteristics of the findings of anemia.

Findings	PLR
Conjunctival rim pallor	16.7
Palmar crease pallor	7.9
Palmar pallor	5.6
Conjunctival pallor	4.7
Pallor at any site	4.1
Facial pallor (but not nail bed pallor)	3.8

Abbreviations: likelihood ratio (LR) if finding present= positive LR (PLR)

Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 8-1, page 91.

What is "the best test for anemia"? The "best test" for anemia is pallor in conjunctiva, palms, face.

- Laboratory
  - Buzzwords
    - Sometimes on multiple choice questions (MCQs), certain terms are used to signal the presence of a particular diagnosis (part of the game of the examiner saying "guess what I'm thinking")

- For each of the following terms (often disguised in Latin or Greek), give the commonly associated hematological condition(s).

Buzzwords	Aka	Hematological conditions
Acanthocytes	- Spur cells	▪ Liver disease, severe
Anisocytosis	- Microcytes	▪ Iron deficiency
Anisopoikilocytosis	- RBC size and shape variations	▪ Iron deficiency
Bile cells		▪ G–6–PD deficiency
Codocytes	- Large cells	▪ Liver disease ▪ Splenectomy ▪ Hemoglobinopathy

Buzzwords	Aka	Hematological conditions
○ Dacrocytes	- Tear drop cells	▪ Bone marrow ▪ Infiltration ▪ Fibrosis ▪ Granuloma
○ Drepanocytes	- Sickle cells	▪ Sickle cell anemia
○ Echinocytes	- Burr cells	▪ Kidney disease
○ Schistocytes		▪ Microangiopathy

Adapted from MKSAP 16, Hematology and Oncology 2012; Table 10, page 18.

Useful definitions

- Tart cell
  - A monocyte or neutrophil which has phagocytosed another cell or nucleus
  - Mimics the LE cell, but occurs in healthy and in disorders with raised immunoglobulins.

- Howell–Jolly bodies: Nuclear remnants seen as small densed purple particles at the periphery of RBCs
  - Causes
    - Splenectomy
    - Dyshemopoietic states: leukemia, megaloblastic anemia, etc

- Pappenheimer bodies: Fe–containing granules in siderocytes
  - Causes
    - Lead poisoning
    - Hemolytic anemia, which continues after splenectomy

- Heinz bodies: Peripheral rounded dark blue bodies in reticulocytes
  - Causes
    - Hemolytic anemia due to drugs and chemicals
    - Familial RBC defects (i.e. G–6–PD deficiency)
    - Rare hemoglobinopathies (i.e. Hb Koln) after splenectomy

- Causes of target cells
  - Iron
    - Iron–deficiency anemia

- Hemolysis
  - Thalassemia
  - Sickle–cell anemia
- Hemoglobin
  - Hemoglobin–C disease
- Liver and spleen
  - Liver disease and obstructive jaundice
  - Splenectomy
- Dehydration

Source: Burton, J.L. *Churchill Livingstone* 1971, page 52.

Pernicious Anemia

- Perform a focused physical examination for pernicious anemia.
  - General
    - Middle age
    - Blue eyes
    - Hair
      - Blondish
      - Prematurely grey
  - Signs of anemia
  - CNS and PNS
    - Mental changes
    - ↓ position and vibration sensation (dorso–lateral column changes)
    - Peripheral neuropathy
  - Eyes
    - Optic atrophy
    - Nystagmus
  - Hepatosplenomegaly
  - Causes of vitamin B12 deficiency
    - Lack of intrinsic factor
      - Pernicious anemia
      - Partial or total gastrectomy
    - Changes in the intestinal flora
      - Stricture
      - Blind–loop syndrome
      - Diverticulosis of small bowel
      - Fistulae

- Ileal damage
  - Crohn's disease
  - Resection
- Parasites: *Diphyllobothrium latum*
- Dietary (rare)
- Pancreatitis (rare)

Abbreviations: UMN, upper motor neuron; LMN, lower motor neuron

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, pages 57 and 58.

Macrocytic Anemia

- Give the causes of macrocytic anemia with normoblastic bone marrow.

  - Nutrition
    - Protein deficiency
    - Scurvy
  - White blood cell
    - Leukemia
  - Red blood cell
    - Hemolysis
    - Hemorrhage
  - Marrow
    - Aplastic anemia
    - Marrow infiltration or replacement
  - Liver
    - Cirrhosis
  - Endocrine
    - Myxedema or hypopituitarism

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 25 and 58.

- Give megaloblastic and 3 non–megaloblastic causes of macrocytic anemia.

  - Megaloblastic
    - Deficiency of folate and/or cobalamin
    - Drugs affecting metabolism of folate and/or cobalamin
    - Myelodysplastic syndromes
  - Non–megaloblastic
    - Chronic liver disease
    - Hyposplenism or asplenia
    - Reticulocytosis

In patient with suspected hemolytic anemia (anemia, ↑ reticulocyte count; ↑ MCV if ↑ reticulocytes, ↑ LDH, ↑ indirect bilirubin, ↓ haptogloblin), the Coombs test is reported to be positive.

- What is Coombs test and the findings if with positive results?
    - Coombs test - A direct antiglobulin test to detect IgG or complement on the surface of RBCs
    - A positive Coombs test - Indicates hemolysis in immune-mediated case

CLINICAL PEARL AND GEMS

- Don't make your patient suffer from vitamin B12 injections when they can easily replenish their body stores of cobalamin by using intranasal or oral (i.e. tablets, gels) treatment.
- In the presence of severe cobalamin deficiency, start at low dose replacement therapy, and consider giving supplements of folate and iron because of their impending rapid demand in response to the ↑ erythrocytosis.
- In patients with folate deficiency and low serum folate concentration, one hardy meal of leafy green vegetables and bananas may be sufficient to correct the low folate concentration, so measure RBC folate on first encounter.
- "Alcohol" (i.e. ethanol) intake can cause macrocytosis and low serum folate concentrations, so either routinely use folic acid supplements, or prove deficiency with ↓ RBC folate and then supplement.
- All patients with hemolytic anemia require daily supplements of folic acid.

Polycythemia

➢ Causes

- Absolute
  - Primary (please see previous section of polycythemia vera)
  - Secondary
    - Hypoxic
      - Intake
        - High altitude (Monge's disease)
        - Cerebral (decreased respiratory drive)
        - Obesity
      - Circulation
        - Cardiac or pulmonary disease
      - Blinding
        - Methemoglobinemia and sulfhemoglobinemia
    - ↑ Erythropoietin
      - CNS
        - Hemangiomas
        - Cerebellar hemangioblastoma
      - Kidney disease
      - Lung bronchial cancer
      - Liver
        - Carcinoma of liver (HCC)
      - GU
        - Uterine myomata
        - Ovarian tumors
    - Endocrine
      - Adrenal cancer and hyperplasia
      - Pheochromocytoma

- Relative
  - Dehydration
  - "Stress" polycythemia

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 62.

  - CNS
    - Hemangiomas
  - Lung
    - Bronchial cancer

- Kidney
  - Renal cancer
  - Benign tumors

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 62.

Hypochromic Anemia

It may be difficult to distinguish between iron deficiency anemia and inflammatory anemia, i.e. in the patient with Crohn's disease. Both will have ↓ serum iron concentration and ↓ transferrin saturation (TS); sometimes the TS may be normal in inflammatory anemia. Both may be normocytic or microcytic (curiously, about a third of patients with iron deficiency will have a normal MCV).

- Give the differences between iron deficiency (FeD) and anemia of chronic disease (ACD).

Cell types	FeD	ACD
Normochromic, normocytic, or hypochromic, microcytic	+	+
Anisocytosis	+	-
Reticulocyte count	↑	↓
Serum iron	N / ↓	N / ↓
TIBC	↑	↓↓
Ferritin	↓	↑
Fe in bone marrow	0	N / ↑
IL–1, IL–6, interferon	N	↑
Hepcidin	↓	↑

Abbreviations: Fe, iron; TIBC, total iron–binding capacity; N, normal

*Note: if a patient has inflammatory anemia and the serum ferritin concentration is > 100 ng/mL, hence, he is not associated with iron deficiency

- Causes
  - ↓ intake of folate, cobalamin (mixture of macrocytes and normocytes)
  - ↓ production
    - ↓ erythropoietin
    - ↓ metabolism
    - Hypothyroidism
    - Testosterone deficiency
  - ↓ release of iron inflammatory blockage (inflammatory anemia, or anemia of chronic disease)
  - Ideopathic

Aplastic Anemia

- Causes
  - Idiopathic
  - Drugs, chemicals (i.e. iodine)

- Clinical

- Give the typical clinical presentation of patient with aplastic anemia.
  - ↓ RBC Fatigue
  - ↓ WBC Fever
  - ↓ platelets Nose bleeds

- Laboratory

- Give the diagnostic tests for pure red cell aplasia (PRCA).
  - PRCA is diagnosed by:
    - CD57+ T–cells on flow cytometry
    - Clonality on T–cell receptor gene rearrangement studies

- What conditions cause aplastic anemia diagnosed on flow cytometry?
  - Lack of expression of CD55 or CD59 on RBC
    - Paroxysmal nocturnal hemoglobulinuria (PNH)
  - Monoclonal CD57–positive T–cell population
    - Acquired chronic red cell aplasia

- Give the hematological complications of parvovirus B19 infection in patient with HIV / AIDs.
  - Chronic pure red cell aplasia
  - Transient aplastic crisis in patient with sickle cell disease

CLINICAL GEM

- The patient with a mechanical heart valve who develops microangiopathic hemolytic anemia from intravascular hemolysis from chemotherapeutic regimens requires an echocardiogram to detect:
  - Valvular regurgitation
  - Paravalvular leakage

Sideroblastic Anemia

- Pathology
  - Iron accumulates in RBC precursors
- Causes of sideroblastic anemia
  - Hypochromic anemia with large numbers of normoblasts containing many iron granules in the marrow
  - Congenital (Pseudothalassemia)
  - Refractory normoblastic anemia of adults
  - Lead poisoning
  - Nutritional
    - B_{12}, folate deficiency, pyridoxine (due to INH therapy)
    -

- Miscellaneous blood dyscrasias
  - Myeloproliferative disease
  - Myelomatosis
  - Collagen disease
  - Carcinoma

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 53.

Sickle Cell Anemia

- Definition
  - Sickle cell disease is a systemic, multiple organ disease which is caused by a point mutation and single amino acid substitution at the 6th position of the β–globin chain and leads to disease causation including phenotype diversity within a given genotype
  - Sickling Syndrome
    - Co–inheritance
      - HbD plus HbS
      - HbE plus β–thalassemia

- Clinical
  - General
    - Vaso–occlusive pain
    - Thromboembolism
    - ↑ risk of infection
    - Multi–organ failure
  - CNS
    - Ischemic stroke
    - Retinopathy
  - CVS
    - Sudden death
  - Lung
    - Acute chest syndrome
    - Pulmonary hypertension
  - Bone
    - Infarcts
    - Osteonecrosis

- GI
  - Hepatopathy
  - Gallstones
- GU
  - Chronic kidney insufficiency (CKI)
  - Priapism
  - Renal medullary carcinoma
- Blood
  - Anemia
  - Aplastic crisis (precipitation by infection with parvovirus B19)
  - Delayed hemolytic transfusion reaction
  - Splenic rupture
- Skin
  - Ulceration
- MSK
  - Aches and pain
    - Needs to rule out veno–occlusive disease

➢ Management
- Ensure correct diagnosis
- Supportive care
  - Hydration
  - Analgesia
  - O_2 therapy
  - Genetic counseling
- Hydroxyurea
  - Veno–oclusive pain episodes
    - Morphine, hydromorphone
    - Patient controlled analgesia (PCA)
    - NSAIDs
  - Acute chest syndrome
  - Anemia, symptomatic
  - ↓ Mortality rate
  - ≥ 2 pain episodes per year
  - ACS
  - No hydroxyurea during pregnancy (teratogenic; stop at least 3 months before planned pregnancy)

- Transfusions
  - Ischemic stroke (CVA)
  - Acute chest syndrome (ACS)
  - Symptomatic anemia
  - Surgery
  - RBC for transfusion in SC disease
    - Leuko reduced
    - HbS negative
    - Matched for E, C, Kell antigens
  - Matched for known alloantibodies
  - Target hemoglobin < 10 g/dL to avoid hyperviscosity
  - Chelation therapy for associated hemosiderosis

- In sickle cell disease, what is the meaning of “Moyamoya syndrome”?
  - Moyamoya syndrome
    - Formation of collateral vasculature due to:
      - Vasculopathy
      - Neovascularization

- What precautions to be done in sickle cell patient requiring blood transfusion?
  - To avoid DHTR
    - Target hemoglobin concentration (Hb) – 100 g/L (10 g/dL)
    - Phenotypic matching of RBC for CCK antigens and any other antigens to which there is alloantibody
  - To avoid veno–occlusion
    - HbS negative blood
  - To avoid GVHD
    - Irradiation of RBC

Abbreviation: DHTR, delayed hemolytic transfusion reactions

○ RBC or erythrocyte exchange transfusion (EET)	- Ischemic stroke (CVA)
	- Acute chest syndrome (ACS)
	- Pulmonary hypertension
	- Hepatopathy
	- Multi–organ failure
	- Priapism
	- Symptomatic chronic anemia
	- Aplastic crisis
	- Skin ulcers
	- Therapeutic
	  ▪ Acute CVA
	  ▪ Fat embolism
	- Prophylactic
	  ▪ History of ischemic CVA

○ Aspirin	- Ischemic stroke
○ O_2, incentive spasmetry	- ACS bronchodilators
○ Empiric antibiotics	- ACS - Associated infection - Target Hb > 100 g/L (10 g/dL)
○ Joint replacement	- Osteonecrosis
○ Erythropoietin	- Severe anemia - Chronic renal disease

CLINICAL GEM

Patients infected with parvovirus B19 often have fever, arthralgias and ↓ reticulocyte count

➢ Sickle cell disease in pregnancy – please see pages 137, 138

➢ Laboratory

- From the reticulocyte count, differentiate the 3 causes of sudden worsening of anemia in patients with sickle cell disease.

	Causes	Reticulocyte count
Aplastic crisis	Parvovirus B19 infection	↓
Megaloblastic crisis	Folate deficiency	↓
Hyperhemolytic crisis	Unknown	↑

- Give the laboratory methods to diagnosis parvovirus B19 infection.
  - IgM antibodies against parvovirus B19
  - Polymerase chain reaction (PCR) detection of parvovirus B19 DNA
  - When patients with sickle cell anemia become infected with parvovirus B19, there is ↓ production of RBCs and aplastic crisis
  - In hereditary spherocytosis, parvovirus B19 may also cause a transient aplastic crisis

➢ Differential

- Sickle cell disease is a greater mimicker. Differentiate the manner of sickle cell disease from the following:

  - Lung
    - Pneumonia
      - Diffuse rather than localized infiltration
    - Fat embolus
      - Fat bodies in bronchial washings or sputum
    - Pulmonary embolus
      - CT chest or angiography gives different pattern

  - Gallbladder
    - Cholecystitis vs. hepatic crisis
      - Abdominal ultrasound will exclude bilirubin stones
      - ↑↑ transaminases in ischemic hepatitis

- Simple anemia of sickle cell disease vs. aplastic crisis or hyperhemolysis
  - In crisis
    - ↓ Hg ≥ 2 g/dL
  - Aplastic crisis
    - Cytotoxic drugs, parvovirus B19, idiopathic
    - ↓ Reticulocyte count
  - Hyperhemolysis
    - ↑ bilirubin, ↑ LDH, ↑ transaminases
    - ↓ reticulocyte count
    - *Mycoplasma* infection
    - Transfusion reaction
    - Associated reaction
    - Associated G6–PD deficiency
- RLQ sickle cell pain vs. appendicitis
  - Fever, tenderness, pain, ↓ bowel sounds, ↑ WBC → Appendicitis
  - ↑ LDH, normal bowel sounds → Sickle cell disease

- What simple laboratory test will help to confirm a patient with sickle cell anemia is adhering to the recommended hydroxyurea treatment?
  - ↑ mean cell volume (MCV) suggests that this RNA–reductase inhibitor (hydroxyurea) is being taken
  - Team approach because of ↑ mortality for
    - Homozygous SS ~ 2%
    - Compound heterozygotes (5 plus B–thalassemia or HbC) ~ 1% trait – normal complication rate
  - Complications
    - ↑ mortality
    - Menarche later
    - First pregnancy later
    - ↑ fetal loss
    - ↑ number of low–birth weight neonates

- Treatment

In patient with sickle cell disease who is known to have alloantibodies and needs blood transfusion, how will the risk of DHTR be reduced?

- Transfuse phenotypically matched RBCs

Acute Chest Syndrome

- Definition
  - Dyspnea
  - Fever
  - Hypoxia
  - New infiltrate in chest X–ray (usually on entire lung segment)
- Causes
  - Infection
  - Infarction
  - Infiltration: fat embolization

- Give the treatment of acute chest syndromes in sickle cell disease.
  - IV hydration (do not over hydrate)
  - O_2
  - RBC transfusion if hypoxia persists
  - Exchange transfusion if hypoxia still persists
  - Bronchodilators for patients with reactive airway disease
  - Incentive spirometry
  - Pain control
  - Empiric antibiotics
  - Avoid overhydration
  - Note – hydroxyurea is useful long–term management to ↓ the risk of acute chest syndrome, but is **not** useful in acute setting.

- Give the treatments which ↓ the risk of acute chest syndrome (ACS).
  - Outpatient - Hydroxyurea
  - Inpatient - Incentive spirometry

- Why meperidine is not the first choice analgesic for pain in sickle cell crisis?
  - Meperidine is metabolized to normeperidine
  - Normeperidine accumulates as a toxic metabolite
  - Normeperidine lowers the seizure threshold
  - Hemoglobin electrophoresis allows the identification of abnormal hemoglobin which arises from single–base substitution of the B gene
  - Hemolytic and aplastic crisis may arise from parvovirus B19 infection
  - Deformed sickle RBCs block small vessels, and thereby cause the disease

Pearls and Gems

- Why opioids are preferred over meperidine for pain management in sickle cell crisis?
  - The metabolic product of meperidine is normeperidine
  - If normeperidine accumulated, the patient may have seizure
- Give the contraindications in the use of hydroxyurea.
  - Pregnancy
  - Renal failure

Patients with chronic hemolytic anemia require daily supplements of folic acid, as well as periodic RBC transfusions.

- Give specific therapies for the causes of hemolytic anemia.
  - Plasma exchange
    - TTP
  - HSCT
    - Severe thalassemia
    - Severe PNH
    - Autoimmune hemolytic anemia not responding to corticosteroids
  - Splenectomy*
    - Hereditary spherocytosis
    - Transfusion–dependent thalassemia
  - Autoimmune hemolytic anemia (warm–body and cold agglutinin) corticosteroids → splenectomy → immune suppression, immune globulin, rituximab, danazol

Abbreviations: HSCT, human stem cell transplantation; PNH, paroxysmal nocturnal hemoglobinuria; TTP, thrombotic thrombocytopenic purpura

*Note:

- Vaccinations are needed before splenectomy
- These vaccinations include:
  - Pneumococcus
  - *Haemophillus influenzae* type B
  - Influenza
  - Meningococcus

Tricks and Red Herrings

A Glucose–6–phosphate dehydrogenase (G–6–PD) deficiency may cause hemolytic anemia.

- When will G–6–PD activity be normal and leads to a false–negative test result for G–6–PD deficiency?
  - During an acute hemolytic episode, the G–6–PD level may be normal
  - Wait for 2 – 3 months after an acute hemolytic episode to measure G–6–PD activity in attempting to diagnose G–6–PD deficiency.

HEMOLYSIS

Hemolytic Anemias

- What clues from the blood tests will say that anemia is of hemolytic in origin?
    - ↑ reticulocytes, indirect bilirubin, lactate dehydrogenase; hemoglobinuria
    - ↓ haptoglobulin

- Conditions to be considered:

➢ Congenital
- Hereditary spherocytosis
- Glucose–6–phosphate dehydrogenase (G–6–PD) deficiency
- Thalassemia syndrome
- Sickle cell syndrome

➢ Acquired
- Autoimmune
- Warm autoimmune
- Cold agglutinin disease
- Microangiopathic
- Paroxysmal nocturnal hemoglobinuria (PHN)

➢ Clinical

- Take a directed history for the causes of hemolytic anemia.
    - Paroxysmal nocturnal hemoglobinuria
    - Hemolytic disease of the newborn
        - Rhesus
        - ABO
    - Inherited
        - Hereditary spherocytosis, elliptocytosis
        - Hereditary non–spherocytic anemia
        - Thalassemia and Thal–like disorders
        - Sickle cell disease and S.C.disease–like hemoglobinopathies

- Immune
  - Idiopathic (warm or cold antibodies)
  - Viral or mycoplasma infection
  - Paroxysmal cold hemoglobinuria (syphilitic or non–syphilitic)
- Infiltration
  - Hematological
    - Malignant disease of lympho–reticular system
  - Solid
    - Myeloproliferative disorders
    - Carcinomatosis
    - Ovarian tumors
    - Atrial myxoma
- Infections
  - Bacterial
    - Coccal septicemia
    - *Clostridium welchii*
    - Oroya fever
    - TB
    - Typhoid
    - "*H. influenzae*" meningitis
  - Protozoal
    - Malaria (Blackwater fever)
    - Kala-azar
- Renal
  - Chronic renal failure
  - "Hemolytic–uremic" syndrome (infants and children)
  - Thrombotic thrombocytopenic purpura (TTP)
  - Malignant hypertension
  - Eclampsia, or postpartum
- Pregnancy
- Endocrine disease
  - Myxedema
  - Hypopituitarism
  - Hypoadrenalism
- Hypersplenism

- Liver disease
  - Hepatitis
  - Cirrhosis
- Inflammatory
  - Crohn's disease, ulcerative colitis
- Immune
  - SLE
- Nutritional
  - Protein deficiency
  - Scurvy
  - Megaloblastic anemia
- Trauma
  - Cardiac surgery
  - March hemoglobinuria
  - Burns
  - Radiation

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 54.

Hereditary Spherocytosis

- Demography
  - 50 / 10^5 Northern Europeans
  - Autosomal dominant with penetrance, or sporatic
- Pathophysiology
  - Mutations in anchoring proteins, i.e. ankyrin leading to destabilized spherocytic cells
  - May be associated with an aplastic crisis when there is an associated parvovirus B19 infection
- Diagnosis
  - Negative direct Coombs test
  - Positive osmotic fragility test
- Treatment
  - Vaccination
    - Pneumococcus, Meningococcus
      - *H. influenzae* type B
    - Splenectomy

Paroxysmal Nocturnal Hemoglobulinuria (PNH)

- Definition
  - Clonal stem cell disorder associated with mutations in PIGA gene which lead to:
    - ↓ glycosylphosphatidylinositol (GPPI)
    - ↓ CD55 (decay–accelerating factor) } GPPI–dependent complement regulatory protein
    - ↓ CD59 (membrane inhibitor of active lysis) } GPPI–dependent complement regulatory protein
  - Results in thrombosis in vascular beds such as cerebral and mesenteric vessels

- Clinical

- Give the clinical presentations of paroxysmal nocturnal hemoglobulinuria.

  - Iron deficiency (from hemoglobulinuria)
  - Hemolytic anemia
  - Pancytopenia (end aplasia)
  - Venous thrombosis (include venous thrombosis of mesenteric vessels)

- Treatment
  - Transfusion of RBC
  - Immunosuppression plus anti–thymocyte globulin and cyclosporine
  - Eculizumab
  - Anticoagulation
  - Human stem cell transplantation (HSCT)
  - Anticoagulation
  - Iron and folic acid

  - Thrombotic events
    - Acute
    - Preventive
      - Anticoagulate
      - Anticoagulation if > 50% of RBC are deficient in CD55 or CD59

- Vaccination for meningococcus, followed by:
  - Eculizumab
  - Immunosuppression
  - Allogenic bone marrow transplantation
- Severe unresponsive hemolytic or aplastic anemia
  - Corticosteroids
  - Iron
  - Erythropoietin

➢ Prognosis
- ↑ mortality rate from:
  - Thromboembolism
  - Progressive pancytopenia

CLINICAL PEARL AND GEMS
- The presence of anemia, microcytosis, ↓ SI, ↓ % TIBC saturation, ↓ ferritin and ↑ sTR and ↓ hepcidin, suggest iron deficiency anemia.
  - In "anemia of chronic disease" (inflammatory anemia), there may be no obvious associated inflammatory process, but remember that the inflammatory cytokines (IL–6, IL–1, interferon) are increased in chronic heart failure and diabetes
  - If hemoglobin concentration is < 8 g/dL, anemia is probably not sTR from a chronic disease association
  - sTR is usually normal in inflammatory anemia, and there is usually sustainable iron in the bone marrow
  - RDW may be normal in inflammatory anemia and, ↑ in iron deficiency

Abbreviations: PNH, paroxysmal nocturnal hemoglobinuria; RBC, red blood cell

Glucose–6–Phosphate dehydrogenase (G–6–PD) **Deficiency**

- Definition
  - Mutation in X chromosome leads to inability of RBC to produce nicotinamide adenosine dinucleotide phosphate (NADPH) necessary in maintaining the glutathione in a reduced state.

- Clinical
  - African American variant
    - Acute hemolysis in response to oxidant stressors to
      - Infection
      - Drugs
    - Dapsone
    - Trimethoprim–sulfamethoxazole
    - Nitrofurantoin
    - Peripheral smear
      - Bite RBC
      - Heinz bodies

DIAGNOSTIC CAUTION

"….elevated levels of G–6–PD are found in young reticulocytes [in the African American variant], and G–6–PD levels may therefore be falsely normal during a hemolytic episode" (MKSAP 16, Hematology and Oncology, 2012, page 27)

To assess safety of drugs in patients with G–6–PD deficiency, please refer to:

www.g6pd.org/favism/english/index.mvc?pgid=safe

Thalassemia

- Definition
  - Abnormal synthesis or either α– or β–chains in hemoglobin, leading to abnormal hemoglobin tetrameric structure, and therefore ineffective erythropoiesis as well as hemolytic anemia with target cells.

- Types
  - Two gene mutations lead to a trait, i.e. Thalassemia α– or β– minor
  - Deletion of 3α genes → hemoglobin disease
  - Deletion of 4α genes (homozygous inheritance of double gene deletion) → hydrops fetalis (- - / -)
  - Involvement of α and β chains → β–thalassemia trait (minor),
    - May have ↑ hemoglobin A2 and F
  - Deletion of 4β genes → β–thalassemia major (Cooley anemia)
  - Thalassemia intermedia ↓ but not absent β chain
  - Hb–5α thalassemia may mimic sickle cell disease

- In Thalassemia, what is Mentzer Index and its significance?
  - Mentzer Index: MCV / RBC count
  - When MCV / RBC < 13, suspect β–thalassemia

α–thalassemia trait (minor, - α / - α, or - - / αα) may be mistaken for iron deficiency, especially when the hemoglobin electrophoresis is normal

- What RDW findings used to distinguish thalassemia minor from iron deficiency?

Condition	RDW
Iron deficiency	↑
Thalassemia	Normal

- There are many causes of microcytic anemia. Without having access to the chemical nature of a patient's hemoglobin B–chain (↓ B–chain synthesis → ↓ hemoglobin (Hb) A [α2β2], and increased HbA^2 or HbF, how to diagnose a patient to have β–thalassemia trait?
  - In β–thalassemia trait, there is a microcytic anemia with ↑ RBC count
  - This is reflected in the Mentzer index: MCV / RBC
  - If Mentzer index is < 13, there is strong possibility of β–thalassemia

A normal hemoglobin electrophoresis does not exclude the diagnosis of α–thalassemia trait.

- What laboratory test will make the definitive diagnosis?
    - Studies of the globin gene synthesis

➢ Treatment
- Life–long regular RBC transfusions
- Treatment of the associated iron overload (from the breakdown of transfused RBCs)
- Splenectomy (↓ RBC destruction in spleen, so ↓ RBC transfusion requirements)
- HSCT (curative)

THERAPEUTIC CHALLENGE

Iron overload from multiple transfusions from β–thalassemia but not from hereditary hemochromatosis is treated with iron chelation deferasirox.

- **Give the reason for the different treatment of the iron overload from hereditary hemochromatosis (HH)**
    - When thalassemia is transfusion–dependent, the patient needs the oxygen–carrying capacity of the transfused blood, whereas in HH the phlebotomy is undertaken to remove the excess body iron while the patient's hemoglobin concentration remains unchanged.

AUTOIMMUNE HEMOLYTIC ANEMIAS (AIHA)

➢ Types
- Warm autoimmune hemolytic anemia (WAIHA)
- Cold agglutinin disease (CAD)

- Associations
  - Inflammation
    - Autoimmune conditions
  - Infiltration
    - Malignancy
    - Lymphoproliferative disorders
  - Infection
  - Iatrogenic
    - Drugs and chemicals
- Laboratory
  - Antibodies
    - IgG, 80%
    - IgM, 20%

- Give the anticipated results of direct Coombs (antiglobulin) test in patients with suspected warm autoimmune hemolytic anemia.
  - The direct Coombs
    - Strongly positive
    - Weakly positive
      - IgG
      - Complement

Warm Autoimmune Hemolytic Anemia

- Pathogenesis
  - IgG antibiotics bind to Rh antigens at 37°C, and these IgG antibody–coated RBCs bind to Fc receptors on macrophages in spleen, resulting to partial phagocytosis of RBC membrane and formation of spherocytes.

Diagnosis	WAIHA	B small cell clone	CAD	RBC shape	Antibody	Macrophage binding
Direct Coombs test	+ IgG	+	+	Spherocytes	IgG	Spleen
C3 (complement)	+ in 10%					

- Treatment
  - Prednisone
  - For prednisone non–responders
    - Azathioprine
    - Cyclosporine
    - Cyclophosphamide
    - Danazol
    - Rituximab
    - Splenectomy

Cold Agglutinin Disease (CAD)

- Pathogenesis
  - IgM antibody binds in the cold to RBC membrane, and fixes complement, resulting in RBC cleared by:
    - Binding to macrophages in the liver
    - Intravascular lysis

SO YOU WANT TO BE A HEPATOLOGIST!

- Explain the ↑ risk of acute or DHTR in CAD.
  - IgM antibody titer may become high in warmed blood
  - Alloantibodies may be masked and not detected by the blood bank service technicians
- In cold agglutinin disease, with RBC hemolysis, name 2 common infections associated with CAD during the patient's convalescence.
  - *Mycoplasma*
  - Epstein–Barr Virus (EBV)
- Explain the increase in mean cell volume occuring in CAD.
  - No, the ↑ MCV is not from:
    - Alcohol
    - Liver disease
    - Deficiency of folate and vitamin B12
    - Reticulocytosis
  - In CAD, the RBC are clumped together, hence, mistaken to be big cells with large volumes, but are just simply agglutinated RBCs.

- Treatment
  - Acute disease - Plasmapheresis
  - Chronic
    - Chlorambucil
    - Cyclophosphamide
    - Rituximab
  - RBC transfusion
    - Cautious use of warmed blood
  - Keep the body warm

Microangiopathic Hemolytic Anemia

- Definition
  - Passage of RBC through the vascular system cases fragmentation of the cells, the formation of schistocytes (helmet cells), and intravascular hemolysis.
- Causes (examples)
  - Macrovascular
    - Damaged mechanical heart valve
    - Intra–aortic balloon
  - Microvascular
    - Hemolytic uremic syndrome (HUS)
    - Thrombocytopenic purpura (TTP)
    - Disseminated intravascular coagulation
  - Pregnancy and liver disease
    - HELLP syndrome
    - Pre–eclampsia
  - Kidney
    - Sclerodermal renal crisis
  - CVS
    - Hypertension
    - Vasculitis

- Treatment
  - Treat the underlying condition
  - Plasma exchange for TTP–HUS
  - Treat associated iron deficiency
  - Erythropoietin when anemias symptomatic and underlying disease does not respond to treatment
  - Drugs
  - Malignancy

Buzzwords, trivia, and ridiculous MCQs.

If the clinical stem is that of a patient with hemolytic anemia and one of the following phrases, watch out: forewarned is forearmed.

Watch out for	They are thinking about
o Travel to Cape Cod, Nantucket Island or Northern California	- Babesiosis
o Travel to Indonesia, Malaysia	- Malaria
o Travel to South America	- Bartonellosis
o Works in battery factory	- Arsine gas
o Young patient with jaundice, behavioral problems, renal tubular acidosis, Kayser–Fleischer rings	- Wilson's disease (copper–induced hemolysis)

WHITE BLOOD CELLS

- Give the causes of eosinophilia (> 440/mm^3)
  - Allergy
  - Infection: Hookworms, tapeworm, hydatid, ascaris, bilharzias, strongyloides, filaria, trichinella, post–infectious rebound
  - Drugs: penicillin, streptomycin, chlorpromazine

- Skin diseases
  - Scabies
  - Dermatitis herpetiformis
  - Atopic eczema
  - Erythema neonatorum
- Pulmonary eosinophilia
  - Asthma (including aspergillosis)
  - Polyarteritis nodosa
  - Tropical eosinophilia
  - Loeffler's
- Hematological
  - Blood dyscrasias (including eosinophilic leukemia)
- Tumor
  - Malignancy
- Miscellenous
  - Eosinophilic granuloma
- Gastrophilic syndromes
  - Post splenectomy
  - Eosinophilic gastroenteritis

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 61.

- Give the causes of pancytopenia or neutropenia.
  - Marrow infiltration
  - Hypersplenism
  - Deficiency
    - Megaloblastic anemia
    - Iron deficiency anemia
  - Paroxysmal nocturnal hemoglobinuria (PNH)
  - Endocrine
    - Hypo– / –hyperthyroidism
    - Cirrhosis
  - Immune
    - Lupus

- Causes of neutropenia
  - Infection
    - Viral
    - Chronic bacterial
  - Malignant infiltration
    - Carcinomatous metastasis to bone
    - Myelosclerosis
    - Myeloma
    - Malignant lymphoma
  - Non–malignant infiltration
    - Gauchers
    - Niemann–Pick
    - Histiocytosis X

Neutropenia

Congenital Asymptomatic Neutropenia

- Definition
  - Absolute neutrophil count (ANC) between 1.0 to 1.5 x 10^9/L (1000 to 1500/μL)
- Demographics common in:
  - Africans
  - Jews, Yemenites
  - Arabs, especially Jordanian
- No complications; no therapy needed

Febrile Neutropenia

Febrile neutropenia is a medical emergency. After taking blood and urine samples for culture, empiric antibiotics must be started immediately.

- Give the recommended immediate empiric therapy for febrile neutropenia.
  - Piperacillin–tazobactam (penicillin / β–lactamase inhibitor)
  - Cefepime (3rd–generation cephalosporin)

Monocytosis

➢ Causes

- Give the causes of monocytosis (>800/mm^3).
    - Infectious
        - Viral: Infectious mononucleosis
        - Rickettsial: Rocky Mountain spotted fever
        - Bacterial: *Listeria monocytogenes*
        - TB
        - Brucellosis
        - Typhoid
        - Subacute bacterial endocarditis (SBE)
        - Protozoal: Malaria, kala-azar, trypanosomiasis
    - Malignancy
        - Hodgkin's disease
        - Monocytic leukemia

Leukocytosis

➢ Causes (>10,000/mm^3 in adults)

- Physiological
    - Infancy
    - Pregnancy and postpartum
- Infection
- Hemorrhage
- Trauma, burns, surgery
- Myocardial infarction and paroxysmal tachycardia
- Toxins: steroids, digitalis, adrenaline, lead, mercury, carbon monoxide
- Collagen vascular diseases
- Infiltration
    - Tumor
    - Myeloproliferative disorders
- Metabolic disorders: renal failure, gout, diabetic coma, eclampsia
- Miscellaneous
    - Hemolysis
    - Serum sickness
    - Acute anoxia
    - Spider venom

- Give the causes of **myeloid leukamoid reaction** (WBC > 50,000/mm^3 or myelocytes or myeloblasts present in peripheral blood).
    - Infections
    - Malignancy
    - Acute hemolysis
    - Leukoerythroblastic anemia
        - Marble bone disease (Albers–Schönberg)

- Give the causes of **lymphocytosis** (> 3500/mm^3).
    - Infections
        - Viral: infectious mononucleosis, infective hepatitis, infectious lymphocytosis, influenza, exanthemata
        - Bacterial: pyogenic infections in young children, convalescence from acute infections, pertussis, typhoid, brucellosis, TB, Syphilis
        - Protozoal: toxoplasmosis
    - Infiltration
        - Lymphocytic leukemia
        - Carcinoma
        - Myeloma
    - Endocrine
        - Myasthenia gravis
        - Thyrotoxicosis
        - Hypopituitarism
    - Physiological (in early childhood)

- Give the causes of **agranulocytosis**.
    - Drugs
    - Aplastic anemia
    - Leukemia in subleukemic phase
    - Hypersplenism
    - Idiopathic

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, pages 59 to 61.

LEUKEMIA

To be covered here:

- Chronic lymhocytic
- Hairy cell
- Acute lymphoblastic
- Acute myeloid

- A patient with acute leukemia has > 25% blast cells in the bone marrow. How can a cell line be diagnosed, and give the appropriate therapy.

  - Lymphocyte lineage may be diagnosed as lymphoid based on markers:
    - B–cell ▪ CD10+, CD20+
    - T–cell ▪ TdT+

  - Induction therapy
    - Anthracycline
    - L–asparaginase

    Corticosteroids

    Vincristine

Chronic Lymphocytic Leukemia (CLL)

- Types
  - B–cell CLL — Western countries
  - T–cell CLL — Asian counties
- Clinical stages
  - ↑ lymphocytes, no symptoms

    I Lymphadenopathy

    II Splenomegaly

    III Anemia

    IV Thrombocytopenia

➢ Diagnosis and prognosis

- Give the tests used to establish the prognosis of CLL.

  - Clinical stage
  - Lymphocyte doubling time
  - Serum B2–macroglobulin concentration
  - Immunophenotyping
  - Cytogenic studies
  - Fluorescence in situ hybridization (FISH) testing
  - Mutational gene

➢ Treatment

o Indications	- Symptoms - Poor prognosis
o Molecular profiling	- High - Likely responsiveness to purine analogue - Fludarabine (purine nucleoside analog) – based chemotherapy plus rituximab - Low likely response to purine analogs
o Other immunotherapy	
o Transformation to large–cell lymphoma	- R-CHOP
o HSCT	- Curative, but ↑↑ risk of morbidity and mortality

➢ Complications

- Give the complications of CLL and its treatments.

o Immune	- Hemolytic anemia - Thrombocytopenia

- Infection
  - *Pneumocystis jiroveci*
  - Cytomegalovirus (CMV)
  - Herpes simplex virus (HSV)
- Blood disorders
  - Hypogammaglobulinemia
  - Monoclonal gammopathies
- Transformation to
  - Large–cell lymphoma
  - Pro–lymphocytic leukemia

Hematopoietic Stem Cell Transplantation (HSCT**)**

- Types
  - Autologous
  - Allogenic
    - HLA–matched donor
    - Unrelated donor
- Preparative
  - ↑ $CD34^+$ stem cells in circulation with G–CSF
  - Conditioning therapy for recipient
    - Myeloablative dose of cytotoxic chemotherapy, +/-
    - Whole body irradiation
  - Facilitate stem cell graft, and ↓ risk of graft–versus–host disease

    Immunosuppression

Hairy Cell Leukemia (HCL)

- Definition
  - Peripheral smear
    - Atypical lymphoid cells
    - Cytoplasmic projections giving lymphoid cells appearance of being “hairy”
    - CD11 and CD103 expression
  - Bone marrow
    - Fibrotic

- Associated hematological changes
  - Hemolytic anemia (HA; direct Coombs positive; warm autoantibody HA)
  - Idiopathic thrombocytopenia (ITP)
  - Transformation
    - Large nodes, spleen, liver

- Suspect in older men with:
  - Cytopenia
  - Splenomegaly (no lymphadenopathy)

- Diagnosis
  - Peripheral smear
    - Mature lymphocytes > 5000/μL
    - "smudge" lymphocytes, distorted lymphocyte
    - B–cell expression of CD19 and CD20
    - T–cell expression of CD5
  - Bone marrow aspiration
  - Atypical lymphocytes with thread–like cytoplasmic projections from the surface of cells
  - Immunohistochemistry

- Treatment

CLINICAL GEM

Older patient, splenomegaly and pancytopenia but no lymphadenopathy: think of hairy cell leukemia. Think cladribine

- Therapy
  - Asymptomatic
    - Follow–up
  - Complicated
    - "B" symptoms (i.e. fever, night sweats)
    - Advanced disease
    - Large–tumor burden
    - Repeated infections

- Drugs
  - Young
    - Cladribine (parenteral purine analog)
    - Fludarabine, cyclophosphamide plus rituximab
  - Older
    - Chlorambucil
- HSCT
  - Resisting or relapsing CU
  - Transformation
- Radiation
  - Painful lymphadenopathy
- Splenectomy
  - Unresponsive
    - Cytopenia
    - Symptoms

Acute Lymphoblastic Leukemia / Lymphoma (ALL)

- Definition
  - ALL is a malignancy of B or T lymphocytes, with ≥ 25% lymphoblasts in bone marrow

- Causes
  - Young age
  - Aggressive disease precursors of T– or B–cells

- Clinical
  - Bone marrow involvement → cytopenia
  - CNS involvement
    - Common (30%)
  - Mediastinum
    - Bulky nodes
  - Less usual presentations
    - Anterior mediastinal mass
    - Superior vena cava (SVC) syndrome
    - CNS involvement

SO YOU WANT TO BE A HEMATOLOGIST!

- Give the physiologic importance of ↓ hepcidin concentration in iron deficiency.
  - When hepcidin is low, ferroportin in duodenal enterocytes traffics to the basolateral membrane and facilitates the transfer of luminal (dietary) non–heme iron to the portal venous blood
  - Also, in the presence of ↓ hepcidin, iron can be released from macrophages and used by bone marrow for the production of erythrocytes.

The measurements of serum levels of vitamin B12 (cobalamin) do not reflect early deficiency in the body stores.

- Give 2 serum markers which reflect body stores and early deficiency of cobalamin.
  - ↑ homocysteine
  - ↑ methylmalonic acid (MMA)
  - Half marks for
    - ↑ lactate dehydrogenase (LDH)
    - ↑ bilirubin

➢ Treatment
- Induction chemotherapy plus HSCT
- Bulky lymphadenopathy
  - Radiation
- CNS prophylaxis
  - Intrathecal chemotherapy, +/- radiation

Acute Myeloid Leukemia (AML)

➢ Cause
- Malignant clonal proliferation of myeloid cells
- Primary
- Secondary
  - Radiation
  - Chemotherapy
  - Benzene
  - Transformation
    - Myeloproliferative disorder (MPD)
    - Myelodysplastic syndrome

➢ Clinical

Pearl and Gem

- Enlarged nodes, spleen and liver rarely occur in AMC
- Common development of thrombocytopenia
- Leukostasis syndrome
  - ↑↑↑ WBC (> 50,000/μL) causes ↓ blood flow → tissue hypoxia
    - CNS
    - Lung
- Tumor lysis syndrome: treatment of AMC may be associated with ↑ release of cellular:
  - K+
  - PO4-
  - Uric acid

➢ Diagnosis

- Peripheral blood smear
  - ↑ WBC
  - ↓ RBC
  - ↓ platelets
  - ↑ Myeloblasts
    - CD34
    - HLA–DR
    - CD33
    - CD13
  - Auer rods: rod–shaped inclusion in myeloblast
- Bone marrow
  - > 20% blasts
  - Cytogenetic studies
    - Prognosis
  - Good
    - T(8;21), t(15;17), INV(16) or t(16;16)
  - Poor
    - Loss or deletion of chromosome 7

Punctuate translucencies in the skull vault are seen in patients with hyperparathyroidism.

- Give a systematic approach to the causes of mottling in the skull.
  - Cancer
    - Metastases
    - Leukemia
    - Myeloma
  - Hematological disorders
    - Sickle cell anemia
    - Histiocytosis X
  - Endocrine disorders
    - Cushing disease
    - Hyperparathyroidism

➢ Treatment

- IV fluids
- Filtered and irradiated platelet transfusion for:
  - Hemorrhage
  - Platelets < 10,000/μL
- Cytarabine and anthracycline
- CD33+ AML: gemtuzumab ozogamicin (relapse in older patients)
- t(15;17): translocation in acute promyelocytic leukemia
  - All–trans–retinoic acid (ATRA)
- Tumor lysis syndrome
  - Prevent
    - Allopurinol plus rasburicase
  - Treat
    - Hemodialysis for acute kidney injury (AKI)
- Leukostasis syndrome
  - Leukapheresis

The t(15;17) translocation found on cytogenetic studies is associated with a good prognosis, but these patients with **acute promyelocytic leukemia** have an abnormal receptor for retinoic acid which ↑ risk of fibrinolysis, DIC and bleeding.

- In AML and acute promyelocytic leukemia, what is **retinoic acid syndrome**?
  - Patients with acute promyelocytic leukemia are treated with ATRA
  - ATRA may lead to:
    - Fever
    - Lung symptoms
    - Hyperleukocytosis and leukostasis syndrome
    - Treat with dexamethasone

SO YOU WANT TO BE A HEMATOLOGIST!

- Give the differences between ALL and AML on cytochemical staining and flow cytometry.

Tests	ALL	AML
Terminal deoxynucleotidyl transferase	+	-
Myeloperoxidase	-	+

- Give the 3 cytogenetic changes in ALL predicting poor prognosis.
  - Hypodiploidy
  - Translocations of ALL gene
  - Philadelphia chromosome (9;22)

Tumor lysis syndrome is common when ALL is treated with rasburicase.

- Why should patient be tested for G–6–PD (glucose–6–phosphate dehydrogenase) deficiency before using rasburicase in ALL?
  - Patient with ALL and G–6–PD deficiency given rasburicase may generate sufficient hydrogen peroxide (H_2O_2) to develop hemolysis or methemoglobinemia.
  - Intrathecal chemoprophylaxis +/- cranial radiation is the standard of care because of the ↑ risk of CNS ALL.
  - If ALL patient is positive for the Philadelphia chromosome, BCR–ABL inhibitors are given, plus cytotoxic chemotherapy.

ATRA–induced differentiation Syndrome

- Definition
  - Treatment for patients diagnosed with acute promelocytic leukemia (APL) with all–trans–retinoic acid (ATRA) or arsenic trioxide release cytokines from the differentiating promyelocytes causes capillary leakage in the lungs resembling non–cardiac pulmonary edema

- Clinical
  - Occurs in first (47%) or third (25%) weeks of treatment
  - Symptoms and chest X–ray suggest pulmonary infection, and antibiotics for possible pneumonia should be given with dexamethasone used to treat the ATRA-inducced differentiation syndrome

MKSAP Resource Site: www.mksap.acpontine.org

HEMATOLOGICAL MALIGNANCY

Lymphoma

- Types
  - NHL - Non–Hodgkin's lymphoma B– (85%), and NK–cell lymphomas
  - HL - Hodgkin's lymphoma

- Associations

	NHL	HL
Immune suppression	++	+
HIV	Anaplastic large–cell	
	Burkitt's lymphoma	
HTLV–1	T–cell	
HCV	B–cell NHL, low–grade	
Drugs (immunosuppresants)	High–grade	
EBV	Burkitt's	+
	PTLD	

  - In a patient with treated HL, there is ↑ risk of NHL!

Abbreviations: EBV, Epstein–barr virus; HIV, human immunodeficiency virus; HTLV, human T–cell lymphotropic virus type 1; PTLD, post–transplant lymphoproliferative disorder

- Diagnosis
  - Exersional biopsy (**not** fine needle aspiration [FNA])
  - Special testing of biopsy material
    - Histology
    - Molecular testing
      - Cytogenetics
      - Fluorescence in situ hybridization (FISH)
      - Gene expression profiling (immunohistochemistry)

- Staging and classification
  - Classification based on mature B–cell, or mature T–cell and NK–cell, as well as numerous other factors
  - For the World Health Organization (WHO) classification of Hodgkin's and non–Hodgkin's lymphomas, please see a standard textbook of medicine, UpToDate, or a recent review such as MKSAP 16, Hematology and Oncology, Table 43, page 99.
  - Phenotypes
    - B–cell
      - Germinal center, prognosis good
      - Activated, prognosis
  - Prognostication
    - Indolent
    - Aggressive
    - Highly aggressive
  - Staging
    - Ann Arbor Staging System
    - International Prognostic Index (IPI) not routinely used anymore
    - Follicular Lymphoma International Prognostic Index (FLIPI)

Follicular Lymphoma

- Useful background
  - Accounts for
    - 20% of all NHLs
    - 70% of indolent NHLs
  - 90% have
    - Rearrangements in Bcl–2 oncogene
    - t(14;18) defect
  - Usually presents with advanced–stage disease, including bone marrow involvement
  - Treatment delayed until there are symptoms or organ dysfunction bone marrow lymph nodes

- Treatment options
  - Rituximab
  - Rituximab plus cyclophosphamide (R–CVP)
  - Rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone (R–CHOP)
  - Rituximab plus bendamustine
  - Tositumomab, **horitumomab** (radioimmunoconjugates)
  - HSCT
    - Autologous
    - Allogene

Abbreviation: HSCT, human stem cell transplantation

- What are the induction and maintenance therapies for indolent non–Hodgkin's lymphoma, follicular lymphoma?

  - Chemotherapy plus rituximab
  - Low follicular lymphoma International Prognostic Index (IPI) – chemotherapy (cyclophosphamide, vincristine and prednisone) plus doxorubicin
  - High follicular lymphoma IPI – chemotherapy (as above) plus rituximab

- Note
  - Radiotherapy may be used for maintenance but not for induction
  - In the absence of symptoms, the patient is followed and not treated, regardless of the extent of the follicular lymphoma

Mantle Cell Lymphoma

- Definition
  - Overexpression of cyclin D1 and t(11;14) translocation on malignant lymphoid cells
- Presentation
  - Usually with stage IV disease involving:
    - Bone marrow
    - Peripheral blood
    - Small intestine
    - Colon
- Diagnosis
  - Histopathology
  - Immunophenotyping
  - Immunohistochemistry
  - Cytogenetic testing
- Therapy
  - Assess therapeutic response with Mantle cell International Prognostic Index (MIPI)
  - Rituximab plus chemotherapy (R–HYPERCVAD)
  - HSCT
    - Allogenic
    - Autologous

Hodgkin's Lymphoma

- Treatment
  - Localized disease — Extended–field radiotherapy +/- chemotherapy
  - Advanced disease — ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine)
  - CD20–positive lymphocyte predominant Hodgkin lymphoma R-ABVD (rituximab plus ABVD)

*poor prognosis factors

  - PET scan positive
  - Age > 45 years
  - Males
  - Hemoglobin < 105 g/L (10.5g/dL)
  - WBC > 15 x 10^9/L (15,000/μL)

Waldenstrom Macroglobulinemia (WM)

- Definition
  - Lymphoplasmacytic lymphoma (≥ 10% of bone marrow cellularity) characterized by production of monoclonal IgM antibodies

- Clinical
  - CNS
    - Peripheral sensorimotor neuropathy
    - ↑ anti–myelin glycoprotein antibodies
  - Blood
    - Platelet dysfunction
    - Anemia
    - Formation of Rouleaux

- Treatment
  - For symptoms WM plus ≥ 10% bone marrow lymphoplasmacytic involvement, or M protein ≥ 3 g/dL
    - Chemotherapy
      - Rituximab (monoclonal anti–CD20 antibody, +/-
      - Cytotoxic agent
    - Alkylating agent
      - Chlorambucil
      - Cyclophosphamide
    - Nucleoside
      - Fludarabine
      - Cladribine

Diffuse Large–Cell Lymphoma

- Most common type of NHL
- B–cell diffuse NHL
  - R–CHOP +/- radiation
    ↓ relapse
    HSCT
- T–cell NHL
  - CHOP

- Diffuse large cell lymphoma is the most common aggressive lymphoma. The initial chemotherapy is R–CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone. Give the treatment of choice for the ~ 50% of patients with recurrence.

  - High dose R-CHOP, plus autologous HSCT

Mucosa–Associated Lymphoid Tissue (MALT) lymphoma

Useful background

- B–cells, CD20–positive
- ~1/2 of all gastric lymphomas

- May be extranodal
  - Eye
  - Salivary glands
  - Thyroids
  - Lung
  - Colon
  - Bladder
- May be limited to spleen but with no lymphadenopathy

➢ Associations
- *Helicobacter pylori* infection
- Autoimmune
  - Sjögren syndrome
  - Hashimoto's thyroiditis

➢ Treatment
- Triple therapy to eradicate *H. pylori*
- Localized MALT
  - Radiation therapy
- Advanced disease
  - Radiation plus rituximab, or
  - R–CVP (rituximab)
- Splenectomy for MALT localized to spleen

Cutaneous T cell NHL

➢ Definition
- T–cell which have
  - CD4 antigen
  - Large "cerebriform" nucleus
  - Clonal T–cell receptor

➢ Clinical
- T–cell NHL of
  - Skin
    - Mycosis fungoides
  - Skin plus blood Sézary syndrome
- Cell–mediated immunodeficiency, with
  - Recurrent bacterial infections
  - Sepsis

- Treatment
  - Early–stage topical
    - Topical
      - Corticosteroids and retinoids
    - PUVA
      - Psoralen and ultraviolet A light
  - Advanced
    - Electron–beam radiation therapy, or
    - Extracorporeal photopheresis
  - Recalcitrant, or involving organs
    - CHOP
    - Alemtuzumab
    - HSCT, allogenic

SPLENOMEGALY

- Definition
  - Hypersplenism
    - Reduction of 1 or more of the formed elements of the blood due to functional hyperactivity of the spleen

- Causes

- Give the causes of splenomegaly.

  - Idiopathic

  - Infections
    - Viral: infective hepatitis, infectious mononucleosis
    - Bacterial: septicemia, SBE, TB, syphilis brucellosis, typhoid
    - Rickettsial: typhus
    - Fungal: histoplasmosis
    - Protozoal: malaria*, kala-azar*, trypanosomiasis
    - Parasitic: hydatid cyst

  - Infiltration
    - Lymphoma
    - Leukemia (especially CML*)
    - Amyloid
    - Sarcoidosis
    - Gaucher, Niemann–Pick disease
    - Benign tumors or cysts
    - Myelofibrosis*

- Immune
  - Rheumatoid arthritis (Felty syndrome)
  - Systemic lupus erythematosis (SLE)

- Hematological
  - Hemolytic anemia
  - Myelofibrosis
  - Polycythemia rubra vera
  - Occasionally in:
    - ITP
    - Myelomatosis
    - Megaloblastic anemia
    - Chronic Fe–deficiency anemia

- Liver portal hypertension

- Endocrine
  - Hyperthyroidism

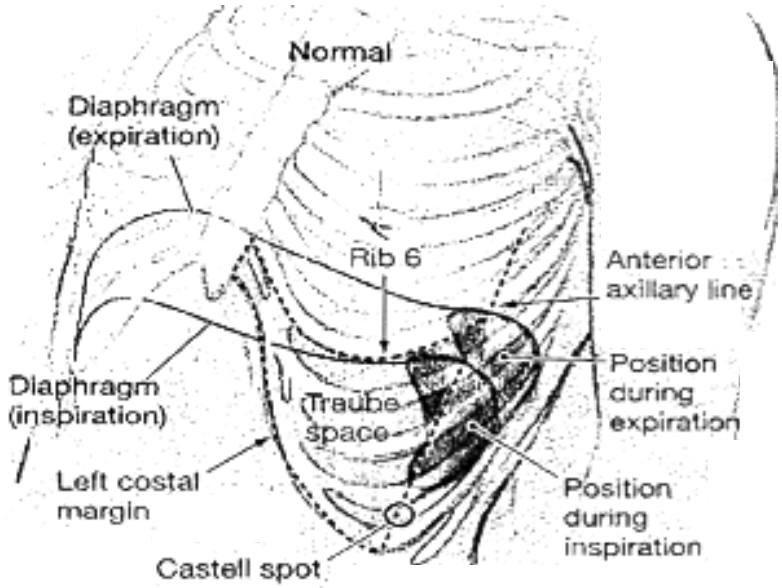
*huge spleen

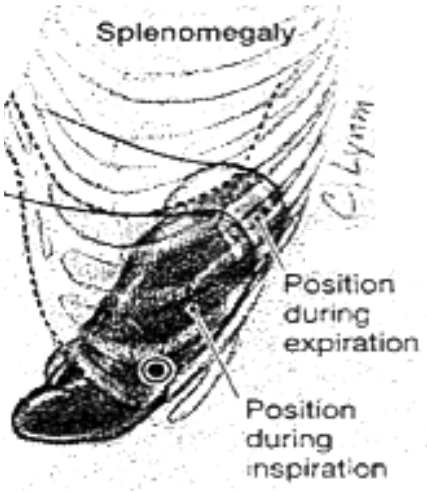
Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 63; and Baliga, R.R. *Saunders/Elsevier* 2007, page 31.

➢ Clinical

- Clinical detection of splenomegaly
  - Several percentage of the normal presumably healthy population may have palpable spleens. The “normal” spleen lies posterior to the left mid–axillary line, and between the 9th and 11th ribs. Normal dimensions are 3 x 7 x 12 cm or less.
  - Because the spleen enlarges anteriorly and posteriorly, spleen size must increase by 40% before becoming palpable.
  - Only a small portion of the spleen protrudes beneath the costal margin, even when considerably enlarged.
  - Inspection should involve asking the patient to breathe in deeply several times as well as looking at the “static” abdomen.

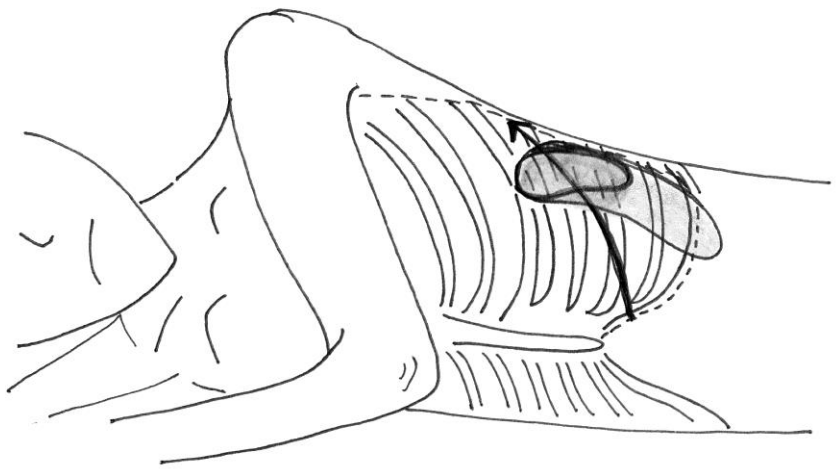
- Percussion in Traube's Space and at Castell's Spot
  - Traube's space is found at the sixth rib superiorly, the left anterior axillary line laterally, and the costal margin inferiorly. Castell's spot is located at the junction of the lowest intercostal space and the left anterior axillary line. The value of Traube's space percussion (TSP) increases when combined with palpation.
  - Castell's sign: Percuss over the lowest intercostal space in the left anterior axillary line while asking the patient to inhale and exhale slowly and deeply. Resonance to percussion on expiration, replaced by dullness to percussion on inspiration suggests splenomegaly.





- Palpation
  - Percussion is more sensitive but less specific than palpation as a diagnostic test for splenomegaly.
  - Percussion (Castell's sign, Traube's space or Nixon method) should be done first, followed by palpation. If both percussion and palpation are positive, the diagnosis of splenomegaly can be ruled in, provided there is a pre–test probability of at least 10%.
  - Done with the patient supine and the knees slightly flexed.
  - Start from the RLQ and work towards the LUQ, again assessing the effect of deep inspiration.
  - Remember that the left hand should not be pulling the spleen forward to the right (examining) hand, but rather pulling the overlying skin forward to give enough slack for the right hand to properly feel under the costal margin.
  - Palpation is most useful in patients who have percussion dullness.

Nixon method to detect splenomegaly



ged spleen

Elee

Pc . margin

  - Discriminate from other masses such as an enlarged kidney:
    - Feel for medial side splenic notching
    - The spleen moves towards the RLQ with inspiration, the kidney moves inferiorly

- Below the costal margin the relatively superficial spleen is dull to percussion; because of overlying bowel the enlarged kidney may sound resonant to percussion
- You cannot interpose your fingers between an enlarged spleen and the costal margin, it is however possible to palpate “above” a kidney.
- You may hear a “splenic rub”.

Adapted from: Simel, D.L., *et al*. *McGraw-Hill Medical* 2009, Figure 46-3, page 607; Filate, W., *et al*. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 34; Davey, P. *Wiley-Blackwell* 2006, pages 82 and 83.

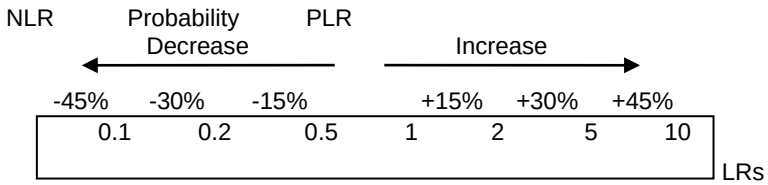
- What factors will increase the pretest probability in finding splenomegaly?
  - Suspected or proven viral illness, lymphoproliferative disorder, or malignancy
  - Cirrhosis (portal hypertension)
  - Suspected or proven malaria
  - Connective tissue disorders associated with splenomegaly

Source: Simel, D.L., *et al*. *JAMA* 2009, page 613.

- Give the perform characteristics for the detection of enlarged spleen.

Findings	PLR	NLR
o Palpation	8.5	0.5
o Percussion	**6.5**	0.2
- Nixon method	2.0	0.7
- Traube’s space dullness	2.1	0.8

Abbreviation: NS, not significant; NLR, negative likelihood ratio; PLR, positive likelihood ratio; MCL, midclavicular line



Note: Castell’s sign has PLR < 2, and is not included here. Also, the spleen examination has a low sensitivity, especially if the pre test probability for splenomegaly is < 10%.

Abbreviation: NLR, negative likelihood ratio; PLR, positive likelihood ratio

Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 47.1, page 554.

Useful background: Performance characteristics for palpation of spleen in various disorders

- Palpable spleen in returning travelers with fever, detecting malaria
- Palpable spleen in patients with non–obstructive jaundice, detecting hepatocellular disease
- Palpable spleen in patients with chronic liver disease, detecting cirrhosis
- Note
  - The likelihood of a high PLR for splenomegaly depends on the clinical setting
  - For example:
    - In a returning traveler with fever where there is splenomegaly from malaria (PLR,6.6)
    - Lower values to detect hepatocellular disease in a patients with non–obstructive jaundice (2.9), or detecting cirrhosis in patients with chronic liver disease (2.3).

Abbreviation: likelihood ratio (LR) if finding present = positive LR (PLR)

Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 47.2, pages 556 -7.

SO YOU WANT TO BE A HEMATOLOGIST!

- Percussion of Traube's space is not specific for splenomegaly. What other conditions cause dullness in this space?
  - Left pleural effusion
  - Large pericardial effusion
  - Massive cardiomegaly
  - Stomach full of food
  - Splenic flexure of the colon due to full of feces
  - Enlarged left kidney

Splenomegaly accompanies hepatomegaly in patients with portal hypertension.

- Give the exceptions to this clinical "rule"?
  - Congenital asplenia
  - Post–surgical asplenia
  - Splenic vein thrombosis
  - Multiple splenic vein infarctions

Amyloidosis (AL; immunoglobulin light–chain amyloidosis)

- Definition
  - β–pleated sheets of protein fibrils of λ and κ monoclonal light chains causing end-organ damage, and associated with multiple myeloma in ~ 10%

- Clinical
  - Major sites of deposit of light chains
    - CNS and PNS
      - Distal sensorimotor neuropathy
      - Autonomic neuropathy
      - Carpal tunnel syndrome
    - CVS
      - Restrictive cardiomyopathy
      - Interventricular septal hypertrophy
    - GI
      - GI tract infiltration
      - Hepatomegaly
      - Macroglossia
    - Kidney
      - Nephrotic syndrome

- Diagnosis
  - Protein electrophoresis and immunofixation
  - IgG λ M–protein
    - Serum
    - Urine
  - Free light chains

- Biopsy pathology
  - Affected organ
  - Combination of fat pad plus bone marrow biopsy
  - Amorphous eosinophilic amyloid protein deposits
  - Apple–green birefringence with Congo red stain examined under polarized light
  - IF / IHC deposits of clonal chains

Abbreviations: IF, immunofluorescence; IHC, immunohistochemistry

- Treatment
  - Melphalan plus dexamethasone
  - Autologous HSCT (less effective than in MM)

SO YOU WANT TO BE A HEMATOLOGIST!

- Perform a focused physical examination of the head and neck for AL amyloidosis.
  - Eyes – "Racoon eyes" from periorbital ecchymosis
  - Macroglossia
- What serological markers for cardiac involvement in AL are predictive of mortality (median overall survival)?
  - Troponin T
  - N–terminal pro–B–type natriuretic peptide

Number of positive serological markers	Median overall survival, months
0	26
1	11
2	4

HEMATOLOGY AND PREGNANCY

To be considered here

- Gestational anemia
- Sickle cell disease
- Gestational thrombocytopenia
- Immune thrombocytopenic purpura
- Microangiopathy of pregnancy
- Thromboembolism in pregnancy

Gestational Anemia

Physiological anemia of pregnancy

- ↑ erythropoietin → ↑ RBC mass
- ↑↑ plasma volume → ↓ blood viscosity

} → ↑ O2 carrying

- ↑ iron requirements for ↑ RBC mass and for fetus
- Parenteral iron in pregnancy

Product	FDA class
Iron dextran	C (presumed uncertain)
Iron sucrose, ferric gluconate	B (presumed safe)

- ↑ folate
  - Requirements for ↑ RBC mass and for fetus
  - To prevent neural tube defects

Sickle Cell Disease in Pregnancy

- Hydroxyurea **not** to be used in pregnancy
  - Stop at least 3 mon before pregnancy–related planned conception
- Team approach because of ↑ mortality for
  - Homozygous SS ~ 2%
  - Compound heterozygotes (5 plus B-thalassemia or HbC) ~ 1% trait – normal complication rate
- Complications
  - ↑ mortality
  - Menarche later
  - First pregnancy later
  - ↑ fetal loss
  - ↑ number of low–birth weight neonates

➢ For more on Sickle Cell Disease, please see pages 88-94.

- Treatment
  - Vaginal delivery
  - For pain
    - Opioids (but not Demerol or Meperidine)
  - For severe anemia with heart failure (HF)
    - Transfusion
  - And say it again
    - **No** hydroxyurea (teratogenic)

- Why meperidine is not the first choice analgesics?

  - Meperidine is metabolized to normeperidine
  - Normeperidine accumulates as a toxic metabolite
  - Normeperidine lowers the seizure threshold

Thrombocytopenia in Pregnancy

Treatment target

- When to give platelets in pregnancy
  - Asymptomatic, PI < 50,000/μL
  - Symptomatic, < 30 – 40,000/μL
  - Cesarean section, < 50,000/μL
  - Neuraxial anesthesia, < 80,000/μL
- Thrombocytopenia in neonate
  - Anti–platelet antibodies may cross the placenta
  - Thrombocytopenia in neonate ~ 10%
  - Problems with measuring fetal platelet levels
    - Scalp vein sampling is misleading
    - Umbilical cord sampling may cause miscarriage (1%)

Gestational Thrombocytopenia in Pregnancy

- A "physiological" effect of pregnancy, due to:
  - ↑ blood volume → dilutional thrombocytopenia
- Suspect pathological causes of thrombocytopenia
  - If platelets < 50 x 10^9/L (50,000/μL)
  - If ↓ platelets in T1 or T2 (first or second terms)

Immune Thrombocytopenic Purpura (ITP) **in Pregnancy**

- ITP is a diagnosis of exclusion; for thrombocytopenia occurring in pregnancy, consider the following:
  - Gestational thrombocytopenia
  - Preeclampsia
  - HELLP
  - DIC
  - TTP

For more on ITP, please see pages 21-22.

Abbreviations: HELLP, hemolysis elevated liver enzymes low platelet count; DIC, disseminated intravascular coagulation

Microangiopathy in Pregnancy

C	T1	T2	T3	Postpartum
	← TTP – HUS →		Preeclampsia	Preeclampsia
	↓		↓ ~ 10%	
	MAHA		HELLP	
	Thrombocytopenia		AFLP	
	↓		↓	
	PE		Delivery	

Abbreviation: AFLP, acute fatty liver of pregnancy; C, conception; HELLP, hemolysis elevated liver enzymes low platelet count; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; T, trimester; TTP, thrombotic thrombocytopenic purpura

Trying to Keep Things Straight regarding Complications in Pregnancy

	MAHA	↓ platelets	PT/aPTT	DIC	↓ BS	↓ SBP	Proteinuria	LE
○ Preeclampsia	-	-	-	-	-	+	+	↑ AT
○ HELLP	+	+	N	-	-	+/-	+	+
○ TTP–HUS	+	+	-	-	-	-	-	-
○ AFLP	-	-	↑	+	+	-	-	↑ Ch

Abbreviations: AFLP, acute fatty liver of pregnancy; aPTT, activated partial thromboplastin time; Ch, cholestatic liver tests; DIC, disseminated intravascular coagulation; HELLP, hemolysis elevated liver enzymes low platelet count; HUS, hemolytic uremic syndrome; MAHA, microangiopathic hemolytic anemia; PT, prothrombin time; TTP, thrombotic thrombocytopenic purpura

CLINICAL CLUES

- Preeclampsia
  - Half occur T3, ~ half postpartum
  - 10% progress to HELLP
- HELLP
  - Half have hypertension
  - Half are normotensive

"Don't judge each day by the harvest you reap but by the seeds you plant"

Robert Louis Stevenson

Thromboembolism in Pregnancy

- ↑↑↑ risk of VTE in 1 – 6 weeks postpartum

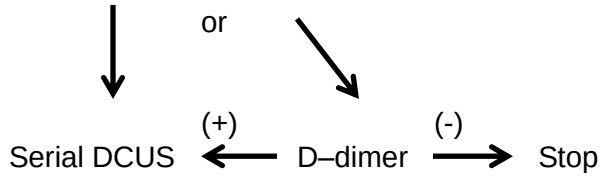
- What is the management for pregnant patient with suspected VTE?

  - Stratify risk

↑ odds ratio	Condition	
↑↑↑↑ (25x)	Previous VTE	Venothromboembolism
↑↑↑ (7-8x)	SLE	Systemic lupus erythematosus
	SCA	Sickle cell anemia
	HD	Heart disease
↑↑ (4x)	↑ BMI	Obesity
↑ (2x)	Anemia	
	↑ age > 35 years	
	DM	Diabetes mellitus
	↑ BP	Hypertension

➢ Diagnosis

  - Duplex compression ultrasonography (DCUS); if DCUS is negative:



  - MRI venography
    - For inferior vena cava (IVC)
  - Ventilation / perfusion (V/Q) scan
  - CT angiography (CTA), abdominal shielding

➢ Treatment

  - VTE in
    - Month 0 – 8 LMWH
    - Month 9 UFH (can easily be reversed peridelivery)

- Vena caval (VC) filter
- Warfarin
  - During (3– 6 months) / after pregnancy (6 – 12 weeks)
  - Okay to use warfarin when nursing

- When is the optimum time to screen a patient with VTE for thrombophilia?

  - It is controversial whether patients should be tested for thrombophilia, but if testing is done, it should be performed months after the acute event and when warfarin has been stopped

- Give the management of the patient with an INR of 1.2 when tested 2 weeks after hospital discharge for VTE.

  - The INR is subtherapeutic, the risk to repeat VTE is high (40% in the first month after VTE, if not properly anticoagulated, and the INR will not be corrected for 3 days after the appropriate ↑ dose of warfarin
  - For these reasons, give LMWH while frequently ↑ warfarin to correct the INR

IMMUNOGLOBULIN DEFICIENCY

➢ Causes

- Give a systematic approach to the causes of immunoglobulin deficiency.

  - Primary
    - Physiological (in infancy)
    - Congenital sex–linked (Bruton)
    - Lymphocytic (Swiss)
    - Lymphopenic (Gitlin)
    - Associated with thymoma (Goods)
    - Associated with thrombocytopenia and eczema (Wiskott-Aldrich)
    - Ataxia telangiectasia (Louis–Bar)

- Secondary
  - Protein deficiency
  - ↓ synthesis
    - Leukemia
    - Lymphoma
    - Myeloma
    - Waldenstrom's macroglobulinemia
    - Irradiation
    - Cytotoxic drugs

➢ Pathophysiology

- In adult, deficiency of serum immunoglobulins may be the result of protein deficiency, hypercatabolic states, or from decreased synthesis from bone marrow disorders, reticuloendothelial neoplasia, or toxic factors. Give 10 causes of secondary immunoglobulin deficiency.

○ ↓ intake of protein	
○ ↓ absorption	- Malabsorption, i.e. celiac disease - Protein–leasing enteropathy
○ ↑ loss	- Nephritic syndrome - Burns - Extensive dermatitis - Pulmonary loss
○ ↓ use	- Hypercatabolic state
○ ↓ synthesis	- Marrow disorders ▪ Metastases ▪ Myelosclerosis ▪ Hypoplasia ▪ Leukemia ▪ Lymphoma ▪ Myeloma ▪ Macroglobulinemia ▪ Hodgkin's disease
○ "toxic" factors	- Irradiation - Diabetes - Thyrotoxicosis - Sepsis - Steroids, cytotoxic drugs

*Note: Any of the above factors may worsen a primary immunoglobulin deficiency.

- Macroglobulinemia occurs in Waldenstrom's macroglobulinemia (WM) as well as in multiple myeloma (MM). What complications of MM are rare in WM?
    - Kidney
        - Chronic renal failure
    - Bone
        - Hypercalcemia
        - Osteolytic bone lesions
        - Amyloidosis

➢ Clinical

- When to suspect MM in WM?
    - Infections
        - Frequent
        - Multiple
        - Prolonged
    - Often due to
        - *Streptococcus pneumoniae*
        - *Haemophilus influenzae*
        - *Neisseria*
    - Consequence
        - Often asymptomatic
        - Infection: *Giardia lamblia*
        - Inflammation
        - False–negative anti–IgA, i.e. anti–tissue transglutaminase (to diagnose celiac disease)
        - Anaphylactic transfusion reaction (from anti–IgA antibodies developed in transfusion recipient)

- In serum immunoglobulins, what are the features of Waldenstrom's macroglobulinemia, and the causes of M–band?

➢ Definition

- An M–band is an increase in serum IgG, IgA or IgM occurring as the result of the increase in one clone of cells to produce increased amounts of only one immunoglobulin
- The single clonal production of increased amounts of immunoglobulin is called "monoclonal gammopathy"

- Waldenstrom's
  - Hepatosplenomegaly
  - Lymphadenopathy
  - Anemia
  - Coagulopathy
  - ↑ macroglobulins
  - ↑ blood viscosity
    - Organ ischemia (i.e. CHF, SOB, retinal bleeding, paresis, neuropathies, myelopathies)

- Causes
  - Idiopathic
  - Myeloma
  - Bence Jones proteinuria without myeloma
  - Heavy–chain disease
  - Leukemia, lymphoma, carcinoma

Selective IgA Deficiency

- Demography
  - Autosomal
    - Recessive, or
    - Dominant, with incomplete penetrance
  - ~ 1:500 persons

- Clinical
  - Recurrent infections
    - Pulmonary
    - GI giardiasis
    - GU, UTI
  - Autoimmune disorders, i.e. celiac disease
  - Atopic disorders
  - Anaphylaxis when given:
    - Immunoglobulin
    - Blood products

- Laboratory
  - ↓↓ IgA
  - May also have
    - ↓ IgG2
    - ↓ IgM
  - Auto–antibodies to IgA

CLINICAL CAUTION

- Why patient with undetectable serum levels of IgA are at risk of transfusion reactions or anaphylaxis when given preparations of immunoglobulin?
  - Patient with selective IgA deficiency may form antibodies directed against IgA and places the patient at risk for blood transfusion of IV immunoglobulins

Common Variable Immunodeficiency (CVID)

- Cause
  - ↓ B cell differentiation
    - ↓ production of immunoglobulins (↓↓ IgG, ↓ IgA, ↓ IgM)
- Clinical
  - Ear, sinuses, eye
    - Infection
  - Lung
    - Bronchiectasis
    - COPD
    - Chronic restrictive pulmonary disease (CRPD)
  - GI
    - Candida
    - *Giardia lamblia*
    - Enteroviruses
    - IDD
    - Celiac disease
  - MSK
    - Rheumatoid arthritis (RA)
  - Blood
    - Hemolytic anemia
    - Thrombocytopenia
    - PA (pernicious anemia)
  - Miscellaneous
    - Non–caseating granulomas
    - ↓ response (to protein or polysaccharide–based)

- Treatment
  - Antibiotic prophylaxis
  - Associated chronic infections
  - Use of > 1 month
    - Corticosteroids
    - Immunosuppressants
  - Immunoglobulins

- What are the usual clinical presentations of common variable immunodeficiency (CVI)?
  - Lung — Sinopulmonary infections
  - GI — Malbasorption
  - Autoimmune disorders
  - Lymphoma

Complement System

- Inherited usually
  - Autosomal recessive; except
  - Autosomal dominant C1 inhibition deficiency
  - X–linked properdin deficiency

- Acquired

- Clinical
  - ↑ risk of infections
  - *Streptococcus pneumonia*e (encapsulated pneumonia)

  3, H, I, properdin
  Neisseria meningitidis, *N. gonorrhoeae*
  Properdin
    - *Neisseria*
    - Recurrent

  Pneumonia
  Otitis media
  - ↑ risk of SLE and other autoimmune disorders
    ↓ C1, C2, C3, C4

- Diagnosis
  - Test for CH_{50} (total hemolytic complement), their specific components

- Treatment
  - Routine conjugate vaccine

INDEX

Note: Page number followed by f and t indicates figure and table, respectively.

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NEPHROLOGY

OVERVIEW

- Give causes of each of the following seen on renal imaging.
    - Measurements
        - Normal long axis length of kidney, 12 – 14 cm
        - Normal difference on length of kidneys, < 1.5 cm
    - Depression and bulging of renal outline
        - Scarring or fibrosis
        - From infection or infarction
    - Decreased renal substance
        - Stenosis
        - Fibrosis
        - Back pressure
        - Old age
    - Causes of bilateral renal swellings
        - Polycystic renal disease
        - Bilateral hydronephrosis
        - Subacute glomerulosclerosis
        - Amyloidosis
        - Leukemia
    - Functions
        - Diluting the urine – loop of Henle
        - Concentrating the urine – collecting ducts
    - Tubular excretory function – H^+, K^+, NH_3^+
    - Tubular reabsorptive function – glucose, PO_4^{2-}, amino acids, water, Na^+
    - Symptoms of hypokalemia
        - Tired
        - Ileus
        - Weak
        - Arrhythmia
        - Renal interstitial fibrosis

➢ Types

- Give the main types of nephropathy.
    - Diabetic
        - Intra–capillary glomerulosclerosis
        - Atherosclerosis
        - Pyelonephritis
        - Papillary necrosis

- Perinephric abscess
  - Frequently bilateral

- Main types of lupus nephropathy
  - Focal necrosis
  - Wire–loop capillaries (thickening of basement membrane of capillaries)

- Complications of asymptomatic bacterial or urinary tract infection – in pregnancy
  - Prematurity of fetus
  - Toxemia
  - Acute pyelonephritis in mother

- Nephrotic syndrome – not associated with uremia or hypertension

SYSTEMIC HYPERTENSION

- Definition
  - Asymptomatic
    - Systolic BP > 200 mm Hg +/- diastolic BP > 120 mm Hg
    - Needs therapy to prevent potential complications of a malignant hypertensive crisis.

  - Malignant hypertension
    - Symptomatic accelerated hypertension (hypertension with end–organ damage)
    - SBP $\geq$ 180 mm Hg, DBP > 100 mm Hg
    - End–organ damage
      - Eye
        - Retinal hemorrhages
        - Optic nerve edema
        - Blurred vision
      - Lung
        - Acute pulmonary edema

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; Cr, Creatinine; CCR, creatinine clearance rate; CVA, cerebrovascular accident; L–CHF, left–sided congestive heart failure

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 145.

- Give the classification of normal blood pressures for adults 18 years or older.

Category	Blood Pressure Level, mm Hg Systolic		Diastolic
○ Normal	< 120		< 80
○ Prehypertension	120 – 139	or	80 – 89
○ Hypertension			
– Stage 1	140 – 159	or	90 – 99
– Stage 2	≥ 160	or	≥ 100

Source: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, Table 14-1, page 425.

- Give the target blood pressure readings at 1 and 4 hours after initiation of treatment in patient with hypertensive emergency.

Time after starting Rx	Target, mm Hg
1 hour	185 / 110 (no more than 25% ↓ in first hour)
4 hours (2 – 6)	160/110

- Take a directed history for the causes of systemic hypertension.
  - Primary
  - Secondary
    - Renal
      - Ischemia
      - Pyelonephritis
      - Glomerulonephritis
      - Polycystic kidney disease
      - Hydronephrosis
      - Diabetes, gout, amyloidosis, nephrocalcinosis
      - Collagen vascular disease
    - Endocrine
      - Pheochromocytoma
      - Hypo–/ –hyperthyroidism
      - Hypercalcemia
      - Hypoglycemia
      - Cushing's syndrome
      - Crohn's disease

- Toxemia of pregnancy
- Heart
  - Coarctation of aorta
- Neurogenic
  - Brain tumor
  - Spinal cord trauma
  - Sleep apnea
  - Porphyria
  - Psyche
  - Anxiety
  - Pain
  - Bulbar polio
  - Head injury
  - Hypothalamic tumor
- Drugs and toxins
  - Alcohol
  - Cocaine
  - Lead poisoning
  - Oral contraceptives
  - Hormone replacement therapy
  - NSAIDs
  - Ephedrine
  - Corticosteroids
  - Monoamine oxidase inhibitors

Abbreviations: CAD, coronary artery disease; CVA, cardiovascular accident; MI, myocardial infarction; NSAIDs, non–steroidal anti–inflammatory drugs; PVD, peripheral vascular disease; TIA, transient ischemic attack

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 14 and Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, pages 48-50, and 172.

- Perform a directed physical examination for systemic hypertension.
  - Eyes
    - Vessels
      - Arteriolar narrowing
      - A–V nicking
      - Hemorrhages
      - Exudates
      - Papilledema

- Retina
  - Papilledema (blurring of disc margins, no venous pulsations)
  - Narrowing and irregularity of arterioles
  - AV nicking
  - Hemorrhages
  - Cotton–wool spots

- CNS
  - Evidence of CVA (effect on cranial nerves, cerebellum, motor or sensory systems)
  - Brain
    - CVA (thrombosis; intracerebral or subarachnoid hemorrhage)
    - Confusion
    - Headaches
    - Seizures

- Neck
  - Thyromegaly
  - Carotid bruits
  - ↑ JVP

- Heart
  - Ischemia
  - Left–sided heart failure (L–CHF)
  - Dissecting aortic aneurysm
  - Left ventricular hypertrophy (LVH)
  - ↑ S2
  - Functional mitral regurgitation
  - Systolic bruit at base of heart, radiating to the right side of neck
  - Bruit due to kinked carotid artery

- Peripheral vasculature
  - Bruits
    - Abdominal aorta
    - Arteries: renal arteries, femoral arteries, popliteal arteries, posterior tibial artery, dorsalis pedis artery
  - Absent or diminished peripheral pulses
  - Ankle to brachial index (peripheral vascular disease or coarctation of the aorta)

- Abdomen
  - Skin
    - Striae of Cushing's syndrome

- Kidney
  - Renal bruits suggesting renovascular hypertension
  - Renal masses to suggest PCK disease
  - Rapid ↑ Cr, ↓ CCR
  - Acute renal failure
- Arteries
  - Abnormal aortic pulsations
  - Femoral bruits to suggest peripheral vascular disease
  - Radio–femoral delay to suggest coarctation of the aorta

- Note:
  - There may be a disconnect between BP and end-organ damage

Abbreviations: AV, aortic valve; CHF, congestive heart failure; CNS, central nervous system; CVA, cerebrovasuclar accident; JVP, jugular venous pressure; LVH, left ventricular hypertrophy; PCK, polycystic kidney disease

Adapted from: Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, pages 172 and 173.

- Take a focused history for complications (end–organ damage) of malignant hypertensive emergency.

○ CNS	- Confusion - Seizures - Headaches - Visual changes - Cerebral thrombosis (TIA or CVA) - Intracerebral or subarachnoid hemorrhage
○ Heart	- Unstable angina - Myocardial infarction - Dissecting aortic aneurysm
○ Lung	- Acute pulmonary edema
○ Kidney	- Acute renal failure
○ Genitourinary	- Severe pre–eclampsia and eclampsia
○ Endocrine	- Pheochromocytoma

Abbreviations: CNS, central nervous system.

Adapted from: Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, pages 48-50 and 172-174.

SO YOU WANT TO BE A CARDIOLOGIST!

- Differenciate Pseudohypertension and Pseudohypotension.
    - Pseudohypertension – artery can be palpated when a blood pressure cuff is inflated to the point of obliterating the radial pulse, and the artery is still palpated as a firm tube in the absence of a pulse (Osler maneuver). Positive Osler sign, indicates the presence of arteriosclerosis, and both SBP and DBP be overestimated.
    - Pseudohypotension – in conditions with high peripheral vascular resistance, i.e. shock, the Korotkoff sounds are difficult to use to measure accurately the systolic or diastolic pressure.

Source: Mangione, S. *Hanley & Belfus* 2000, pages 28 and 29.

- In primary hyperaldosteronism, give the effects of variations in the intake of salt (NaCl) on aldosterone and renin.
    - High salt intake – no effect on aldosterone
    - Low salt intake – no effect on renin

➢ Treatment

- Give the non–pharmacologic therapies to reduce blood pressure in hypertensive patients.
    - Normalize body mass (BMI). If BMI > 25, then reduce weight by at least 4.5 kg, but weight loss to a BMI of between 18 and 25 is preferred.
    - Limit alcohol consumption (a maximum of 2 standard drinks per day for a total of 14 drinks per week for males or 9 drinks per week for females)
    - Exercise (3 – 4 times per week at a moderate level of intensity for 50–60 minutes)
    - Restrict salt (to 90– 130 mmol or 3 – 7 g/day)
    - Smoking cessation
    - Stress management

Abbreviation: BMI, body mass index

Adapted from: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, page 49.

RENAL CALCULI

- Take a directed history for the causes of renal colic.

➢ Clinical

- Pain
  - Location of pain (unilateral *vs*. bilateral, radiation to the groin)
  - Duration
  - Course over time
  - Onset
  - Course (ureteral colic from intermittent ureteral distention, constant flank pain from renal capsular distention)
- Irritative urinary symptoms
  - Increased urinary frequency or nocturia
  - Urgency
  - Dysuria
- Obstructive urinary symptoms
  - Hesitancy
  - Diminished stream
  - Postvoid dribbling
  - Postvoid suprapubic fullness
- Associated symptoms
  - Hematuria
  - Diaphoresis
  - Constitutional (fever and chills or night sweats and weight loss)
  - Abdominal (nausea and vomiting)
- Metabolic syndromes
  - Chronic hypercalcemia
  - Hypercalciuria
  - Hyperoxaluria (idiopathic, genetic [type I or II] or secondary to GI disease)
  - Hypocitraturia (distal renal tubular acidosis, K+ depletion, renal failure)
  - Genetic metabolic diseases (i.e. cystinuria)
- Concentrated urine
  - Chronically low fluid intake (< 2 L/day) or high insensible
  - Structural abnormality
  - Renal tract obstruction (i.e. sloughed papilla, prostate enlargement, neurogenic bladder)
  - Nephrocalcinosis
  - Renal tubular acidosis (distal, type I)

- Risk factors
  - Diet high in oxalates (spinach, rhubarb, nuts, tea, cocoa)
  - Calcium or excess vitamin C administration
  - Prolonged immobilization
  - Meds (chemotherapy, furosemide, hydrochlorothiazide, indinavir)
  - Family Hx of kidney stones
  - Inflammatory bowel disease (Crohn's disease)
  - Recurrent urinary tract infections

- Causes
  - Ca^{2+} hypercalcemia
  - Hypervitaminosis C
  - Oxalates – diet (spinach, rhubarb, nuts, tea, cocoa)
  - Dehydration
  - Urinary tract infection
  - Previous urinary tract infections
  - Drugs (furosemide, hydrochlorothiazide, chemotherapy, indinavir)
  - Inflammatory bowel disease
  - Family history of kidney stones

Abbreviation: GI, gastrointestinal tract

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 255; Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, page 82; Burton, J.L. *Churchill Livingstone* 1971, page 105.

GI DRUGS AND RENAL IMPAIRMENT

- Nephrotoxic: **Avoid!**
  - ASA, NSAIDs
  - Etidronate (bisphosphonates for osteoporosis, i.e. Crohn's disease, celiac disease)
  - Methotrexate (IBD)
  - Penicillamine (Wilson's disease)
  - Ribavirin (NCV)
  - Sucralfate (in high doses)
- Dose reduction
  - Assume ≥ 75% renal elimination for dosage adjustment
  - Azathioprine and Mercaptopurine
  - Diphenoxylate
  - Lamivudine
  - Meperidine
  - Metoclopramide
  - Morphine
  - Octreotide

Adapted from: McCormack, J., *et al*. Appendix 1. In: Therapeutic Choices. Grey, J., Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 1697 to 1719.

NEPHROTIC SYNDROME

- Definition
  - Proteinuria > 0.5-1 g/d, plus a bland urinary sediment (no cells or cellular casts)

- Causes

- Give the causes of nephrotic syndrome.
  - Obstruction
  - Toxins and Drugs: Glomerulonephritis
  - Metabolic
  - Collagen vascular disease
  - Infection
  - Congenital and familial
  - Diseases causing radiologically visible (opaque) nephrocalcinosis and renal stones
    - Diffuse, cortical
      - Chronic glomerulonephritis
      - Old cortical necrosis
    - Coarse, medullary
      - Primary hyperparathyroidism
      - Primary renal tubular acidosis
      - Chronic pyelonephritis
      - Idiopathic hypercalciuria
      - Idiopathic
    - Localized
      - Medullary sponge kidney
      - Renal neoplasm
      - Cysts
      - Papillary necrosis
      - TB
      - Hydatid cyst
    - Radio–opaque
      - Calcium (oxalate, phosphate, mixed)
      - Cysteine
      - Silicate
      - Calcified uric acid stone

For a detailed list of the causes of nephrotic syndrome within each of these headings: please see: Burton, J.L. *Churchill Livingstone* 1971, page 103.

- Diseases causing non–opaque nephrocalcinosis
  - Stone (uric acid, xanthine)
  - Tumor, cyst
  - Clot
  - Papillae
  - Varix

➢ Differential

- Give the differential diagnoses for renal calculi on renal imaging.

- Blood clot
- Sloughed papillae
- Tumor
- Varices

Where is the trick? This question is not about the types of renal calculi, but rather, what may look like a renal calculus that is actually something else.

Source: Burton, J.L. *Churchill Livingstone* 1971, page 106.

ACUTE INTERSTITIAL NEPHRITIS

➢ Causes

- Give the common causes of acute interstitial nephritis.

- Idiopathic
- Infections
  - Bacteria
    - *Legionella*
    - *Brucella*
    - *Streptococcus*
    - *Pneumococcus*
  - Virus
    - Epstein–Barr
    - CMV
    - *Hantavirus*
    - HIV
    - Hepatitis B
    - *Polyomania*
  - Fungus
    - *Candida*
    - *Histoplasma*

- Parasites
  - *Plasmodium*
  - *Toxoplasma*
  - *Schistosoma*
  - *Leishmania*

- Drugs and toxins
  - Antibiotics
    - Penicillin
    - Methicillin (anti–tubular basement membrane antibodies)
    - Ampicillin
    - Rifampin
    - Sulfa drugs
    - Ciprofloxacin
    - Pentamidine
  - NSAIDs
    - Interstitial nephritis with nephritic syndrome and renal insufficiency may have latent period
    - Not dose–dependent
    - Recurs
    - Possibly T–cells mediated
    - Allergic signs and symptoms are absent
  - Diuretics
    - Thiazides
    - Furosemide
    - Bumetanide (sulfa derivatives)
  - Cimetidine
  - Allopurinol, phenytoin, phenindione
- Immune
  - Systemic lupus erythematosus (SLE)
  - Sjögren syndrome
  - Sarcoidosis
  - Renal transplant rejection
- Infiltration
  - Lymphoma
  - Leukemia
- Drugs causing hyponatremia
- SIADH

Abbreviations: ASAs, acetylsalicylic acids; CCF, congestive cardiac failure; CMV, cytomegalovirus; CNS, central nervous system; HIV, human immunodeficiency virus; NSAIDs, non–steroidal anti–inflammatory drugs SIADH, syndrome of inappropriate secretion of antidiuretic hormone

Adapted from: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, Table 18-6, page 703; Davey, P. *Wiley-Blackwell* 2006, pages 250 and 268.

- Give a systematic approach to the causes of interstitial renal fibrosis.

    - Systemic hypertension
    - Electrolytes – hypokalemia
    - Obstruction of ureters
    - Aging
    - Drugs – sulfonamide or acetaminophen (in high doses)
    - Radiation to renal area

RENAL FAILURE

Acute Renal Failure

➢ Causes

- Take a directed history to determine the causes of acute renal failure (ARF).
- Pre–renal
    - HF
        - ↓ intake
        - ↑ losses
            - Vomiting
            - Diarrhea
            - Bleeding
        - Fluid redistribution
            - Internal bleeding
            - Sepsis
            - HF
    - Hypertension
- Renal
    - Glomerulus – acute glomerulonephritis
    - Tubule – ATN
    - Cortex – cortical necrosis (dehydration in children, ante–partum hemorrhage)
    - Renal
        - Glomurulonephritis
        - Nephrotoxic drugs (i.e. gentamycin, NSAIDs)
        - Rhabdomyolysis
        - Interstitial nephritis
        - Myeloma
        - Hemolytic uremic syndrome

- Vascular
  - Hypertension
  - Hypotension (ischemia)
  - Renal artery thrombosis
  - Stenosis
  - IVC thrombosis
  - Fat emboli
- Infection
  - Sepsis
  - Systemic infections
- Metabolic
  - Diabetes
  - Hypothyroidism
  - Hypoadrenalism
  - Hypercalcemia
  - Hyperuricemia
  - Diabetes mellitus
- Liver
  - Hepatorenal syndrome
  - Hypercalcemia
- Pregnancy
  - Toxemia of pregnancy
- Acute collagen–vascular disease
- Acute or chronic (often precipitated by infection or electrolyte disturbance)
- Medications
  - Drugs (aminoglycosides, contrast dyes, NSAIDs, sulfanilamide, thiazides, rifampin, allopurinol, cimetidine, phenytoin, analgesics, chemotherapy)
  - Infections - renal (post streptococcal glomerulonephritis; pyelonephritis)

- Post–renal
  - Ureteric stones (reflux anuria)
    - Retroperitoneal fibrosis
    - Tumors of prostate, bladder, cervix, ureters
    - Benign prostatic hypertrophy (BPH)
    - Reflex anuria due to stones

Abbreviations: ARF, acute renal failure; ATN, acute tubular necrosis; HF, heart failure; IVC, inferior vena cava

Adapted from: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, page 712.

➢ Clinical

- Perform a focused physical examination for the causes of acute renal failure.

  - Acute–to–chronic renal failure (often precipitated by infection or electrolyte disturbance)
  - Acute cortical necrosis
    - Ante–partum hemorrhage
    - Excessive dehydration in children
  - Acute tubular necrosis (ATN)
    - Toxins (i.e. drugs, metals)
    - ”Shock”
    - ”Crush syndrome”
    - Transfusion reactions
    - Heat stroke
    - Acute hemolysis
  - Acute glomerulonephritis
  - Ischemia
    - Renal artery thrombosis
    - Progressive stenosis
    - Inferior vena caval thrombosis
    - Fat emboli
  - Immune
    - Acute ”collagen vascular” disease
  - Infection
    - Acute fulminating
  - Metabolic, i.e. hypercalcemia
  - Pregnancy (Toxemia)
  - Hepatorenal syndrome
  - Reflex anuria due to obstruction (i.e. renal stone)

Abbreviations: ATN, acute tubular necrosis

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 101.

Chronic Renal Failure

- Definition:
  - The stages of chronic disease are described using the glomerular filtration rate (GFR) or creatinine clearance.
  - "Estimates of GFR (eGFR) are calculated and reported using the MDRD formula including age, sex and creatinine, with a correction for block race.
  - Alternatively, an estimated creatinine clearance can be calculated using the Cockcroft–Gault equation….or measured using a 24–hour urine collection.
  - The definition of chronic kidney disease (CKD) is defined as:
    - The presence of kidney damage for > 3 months
    - GFR or eGFR < 60 mL/min / 1.73 m^2, or
    - GFR or eGFR > 60 mL/min / 1.73 m^2 with abnormalities of urine sediment

Wazny, L and Moist, L. Chapter 91. In: Therapeutic Choices. Grey, J., Ed. 6th Edition, *Canadian Pharmacists Association* 2012, page 1266.

- Clinical

- Take a directed history to determine the causes of chronic renal failure.

  - Pre–renal
    - Hypovolemia
    - Sepsis
    - Post surgery
    - Cardiogenic shock
    - Hepaticfailure
    - Drugs (i.e.NSAIDs)
    - Renal artery or vein obstruction
  - Renal
    - Glomerulus
      - Glomerulonephritis
    - Tubule
      - Renal tubular acidosis
      - Chronic hypokalemia
      - Fanconi syndrome (generalized proximal tubular damage)
    - Obstruction
      - Stones
      - Tumors
      - Fibrosis
      - BPH

- Vascular
  - Hypertension
  - Hypotension (ischemia)
  - Hypovolemia
- Infection
  - Chronic pyelonephritis
  - Renal TB
  - Sarcoidosis

- Cardiac
  - HF
- Dehydration
  - Decreased fluid intake
  - Vomiting
  - Diarrhea
  - Excessive sweating
  - Use of diuretics
- Expanded fluid volume
  - HF
  - Cirrhosis
  - Nephrotic syndrome
- Metabolic
  - Diabetes
  - Hypercalcemia
  - Amyloid
  - Hypothyroidism
  - Hypoadrenalism
  - Hyperuricemia
- Medications
  - Phenacetin
  - Radiation
  - NSAIDs
  - Diuretics
- Collagen–vascular
  - Polyarteritis nodosa
  - SLE
  - Scleroderma
  - Wegeners
  - Goodpasteur disease
  - Henoch–Schonlein
  - Hemolytic uremia syndrome
  - Thrombotic thrombocytopenia

- Congenital
  - Polycystic renal disease
  - Hypoplasia

Abbreviations: BPH, benign prostatic hyperplasia; CRF, chronic renal failure; HF, heart failure; SLE, systemic lupus erythematosus; TB, tuberculosis

Adapted from: Ghosh, A.K. *Mayo Clinic Scientific Press* 2008, Table 18-9, page 712; Burton, J.L. *Churchill Livingstone* 1971, page 101 and 102.

➢ Risks

- Give the risk factors for chronic kidney disease.

  - Atherosclerotic vascular disease
  - Autoimmune disease, i.e. lupus, rheumatoid arthritis, connective tissue disease and vasculitis
  - Chronic urinary tract obstruction from prostatic enlargement, neurogenic bladder, kidney stones
  - Chronic viral infections, i.e. Hepatitis B and C, HIV
  - Diabetes mellitus
  - Family history of kidney disease
  - First Nations people
  - Hereditary polycystic kidney disease
  - History of acute kidney injury
  - Hypertension
  - Multiple myeloma
  - Problems in pregnancy including edema, hypertension, proteinuria
  - Recurrent pyelonephritis
  - Reduced nephron mass (i.e. congenital single kidney, post–nephrectomy, scarring from reflux nephropathy)
  - Use of known nephrotoxic drugs (i.e. acetaminophen, NSAIDs including COX–2 specific inhibitors, lithium, cyclosporine, tacrolimus, contrast dyes)

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 2, page 1267.

- Give the stages of chronic kidney disease.

Stages	Definition
○ Stage 1	- Damage with normal GR or GFR > 90 mL/min/1.73 m^2
○ Stage 2	- Damage with GFR 60 – 89 mL/min/1.73 m^2
○ Stage 3	- GFR 30 – 59 mL/min/1.73 m^2
○ Stage 4	- Severe renal dysfunction, with GFR 15-29 mL/min/1.73 m^2
○ Stage 5	- Kidney failure, GFR < 15 mL/min/1.73 m^2

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 1266.

➢ Clinical

- Take a directed history and perform a focused physical examination for chronic renal failure (uremia).

  - CNS
    - Altered mental state
    - Hypertensive encephalopathy
      - Headache
      - Visual disturbance
      - Confusion
      - Coma
    - Epilepsy
    - Mania
    - Focal neurological signs
    - Peripheral neuropathy
  - Heart
    - Increased risk of ischemic heart disease
    - HF
    - Pericarditis
  - Lungs
    - R–CHF from L–CHF
    - Pulmonary edema
    - Pleural effusions
    - Infection
    - Abnormal breathing
      - Cheyne–Stokes
      - Kussmaul breathing

- Hands
  - Nails leukonychia; white lines; distal brown arc
  - Vascular shunts
  - Asterixis
  - Neuropathy
- Arms
  - Bruising
  - Pigmentation
  - Scratch marks
  - Myopathy
- Face
  - Eyes: anemia, jaundice, band keratopathy
  - Fundoscopy: hypertensive and diabetic changes
  - Mouth: dryness, ulcers, fetor
  - Rash (vasculitis)
- Back
  - Tenderness
  - Edema
- Legs
  - Edema
    - Nephrotic syndrome
    - HF
  - Bruising
  - Pigmentation
  - Scratch marks
  - Neuropathy
  - Vascular access
- CNS
  - Headache
  - Lethargy
  - Dizziness and ataxia
  - Mild confusion
  - Psychosis
  - Seizures
  - Coma
- Abdomen
  - Scars: dialysis, operations
  - Kidneys: transplant kidney
  - Bladder
  - Liver
  - Lymph nodes
  - Ascties
  - Bruits

- GI tract
  - Rectal examination (BPH, bleeding)
  - Anorexia, nausea, vomiting
  - Hiccups
  - Diarrhea
  - Furred tongue
  - Stomatitis
  - Gastritis
- Kidney
  - Collagen vascular disease
    - Polyarteritis nodosa
    - Wegener's granulomatosis (granulomatous angiitis)
    - Hypersensitivity angiitis
    - SLE
    - Systemic sclerosis
    - Goodpasture disease
    - Henoch–Schonlein
    - Hemolytic uremic syndrome (HUS)
    - Thrombotic thrombocytopenia of Moschcowitz
    - Radiation nephritis
  - Infection
    - Chronic pyelonephritis
    - Renal TB
  - Metabolic
    - Diabetes
    - Amyloid
    - Gout
    - Hyperparathyroidism
    - Vitamin D excess
    - Sarcoidosis
    - Chronic phenacetin ingestion
    - Milk–alkali syndrome
  - Obstruction
    - Calculi
    - Peri–ureteric fibrosis
    - Neoplasm
    - Prostatic hypertrophy
    - Urethral obstruction
    - Bladder neck obstruction
  - Primary tubular disease
    - Fanconi's syndrome
    - Tubular acidosis
    - Chronic potassium depletion

- Congenital anomalies
  - Polycystic kidney
  - Renal hypoplasia

- Skin
  - Palor (anemia)
  - Purpura
  - Pruritus
  - Macular lesions
  - Uremic frost

- Systemic
  - Fever (even in absence of infection)

➢ Causes

- Glomerulonephritis

- Primary tubular disease
  - Fanconi's syndrome
  - Tubular acidosis
  - Chronic potassium depletion

- Congenital anomalies
  - Polycystic kidney
  - Renal hypoplasia

Abbreviations: BPH, benign prostatic hypertrophy; SLE, systemic lupus erythematosus; TB, tuberculosis; CHF, congestive heart failure

Source: Burton, J.L. *Churchill Livingstone* 1971, page 103.

- Give examples of medications to avoid in late stage chronic kidney disease.

Medications	Complications
Baclofen	Increased neurotoxicity even at very low doses
Magnesium-containing medications, i.e. antacids, laxatives	Magnesium accumulation
Meperidine	Accumulation of an active metabolite that can lead to seizures
Metformin	Risk of lactic acidosis with ClCr < 30 mL/min
NSAIDs, COX–2 inhibitors and nephrotoxins	Increased risk of acute kidney injury

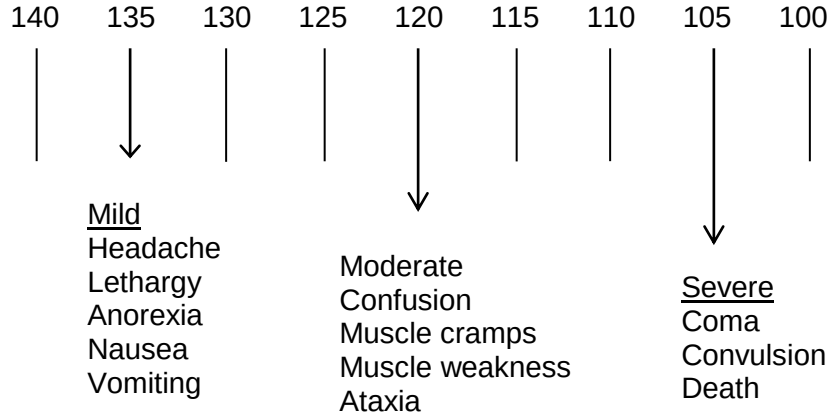
Medications	Complications
○ Phosphorus–containing products (i.e. Fleet Phospho–soda)	- Death due to hyperphosphosphatemia and resulting hypocalcemia has been reported and these products can also cause acute phosphate nephropathy.
○ Potassium–sparing diuretics and herbals such as alfalfa, dandelion, noni juice	- Risk of hyperkalemia
○ Sotalol	- Increased accumulation as renally excreted and risk of torsades de pointes
○ Vitamin A	- Risk of accumulation secondary to decreased renal catabolism and increased serum levels of retinol–binding protein.
○ Vitamin C	- Limit to no more than 60 – 100 mg/day as the metabolite (oxalate) can result in deposits of calcium oxalate in the soft tissues and kidney stones.

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 7, page 1275.

HYPONATREMIA

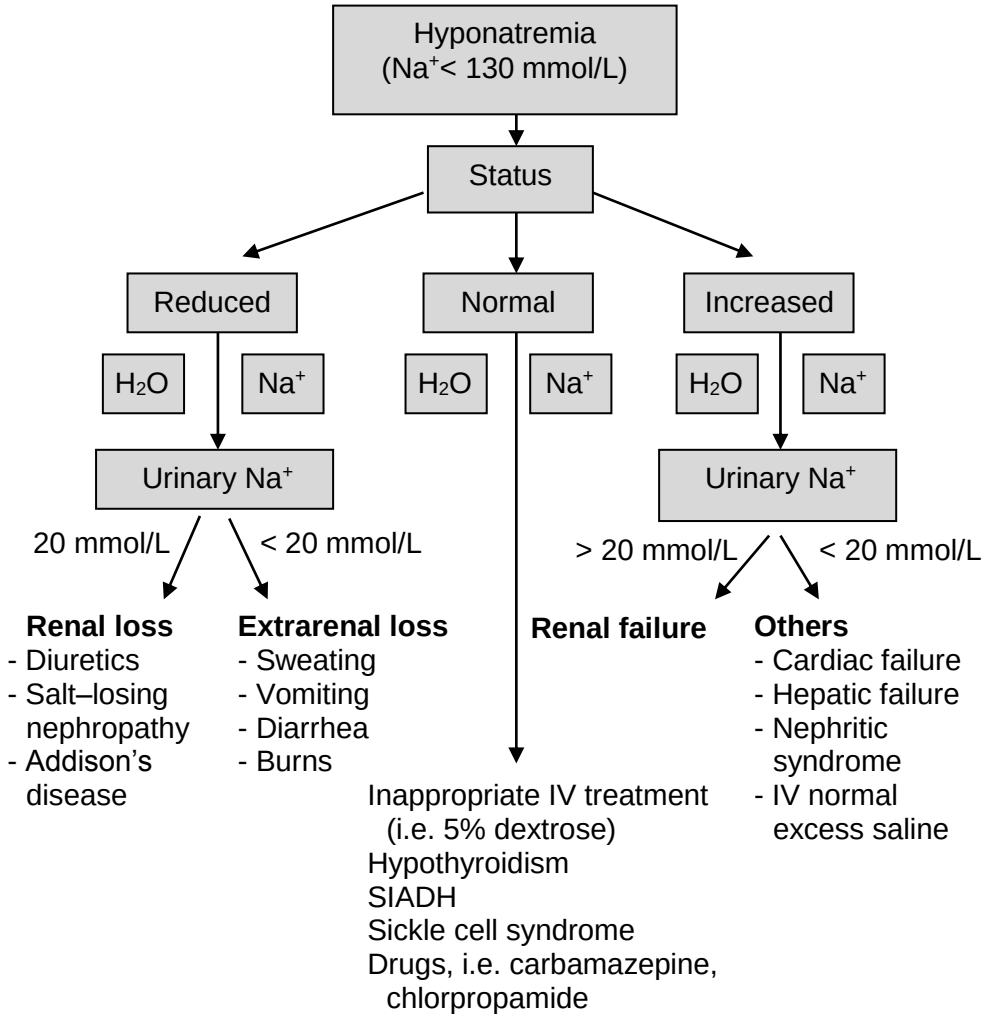
➢ Clinical features of hyponatremia

- Take a directed history for hyponatremia ($[Na^+] < 125$ mmol/L)



Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 250.

Approach to hyponatremia



Abbreviation: SIADH, syndrome of inappropriate secretion of anti–diuretic hormone

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 250.

- Give the clinical and laboratory causes of hyponatremia.

Variable	↓ ECF	Normal / near - normal ECF	↑ ECF
○ Causes	- Diarrhea - Vomiting - Excessive sweating - ↓ water intake - Diuretic use	▪ SIADH ▪ Hypothyroidism ▪ Adrenal insufficiency	- HF - Cirrhosis - Nephrotic syndrome
○ Serum osmolality	↓	↓	↓
○ Urine osmolality, mOsm/L	> 500	> 100	> 100
○ Urine volume	↓	Varies with intake	↓
○ Urine sodium concentration, mmol/L	< 20	> 40	< 20
○ Response to 0.9% saline infusion	- Clinical and biochemical improvement	▪ No change or worsening of hyponatremia	- Little change in hyponatremia; worsening of edema

Abbreviation: SIADH, syndrome of inappropriate secretion of anti–diuretic hormone; ECF, extracellular fluid; HF, heart failure

Source: Yeates, K.E., *et al*. *CMAJ* 2004; 170(3):365-9, Table 1, page 367.

SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONES

- Give the causes of syndrome of inappropriate anti–diuretic hormone (SIADH).

  - CNS
    - Infection
    - Stroke
    - Neoplasia
    - Trauma
    - Alcohol withdrawal
    - Acute psychosis
    - Meningitis
    - Encephalitis

- Lung
  - Infection
    - Viral or bacterial pneumonias
    - Bronchogenic tumor
    - TB
  - COPD + lung infection
- GI
  - Cancer
- Renal
  - Prostate cancer
- Blood
  - Malignancies
- Endocrine
  - Acute intermittent porphyria
- Infection
  - HIV / AIDS
  - ↑ H2O permeability of nephron (i.e. vasopressin)
  - ↑ ADH release (i.e. carbamazepine)
  - ↑ ADH action (i.e. cyclophosphamide)
  - ↓ Prostaglandin synthesis (i.e. aspirin)
- Ideopathic

Abbreviations: ADH, anti–diuretic hormone; AIDS, acquired immunodeficiency syndrome; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; GI, gastrointestinal tract; HIV, human immunodeficiency virus; TB, Tuberculosis

Adapted from: Davey, P. *Wiley-Blackwell* 2006, Table 127.1, page 251.

FLUID AND ELECTROLYTE DISORDERS

- Definitions
  - Hypovolemia
    - General term meaning volume depletion and dehydration
  - Volume depletion
    - Low of salt and water from intravascular space (IVS)
    - Associated with ↓ BP and ↑ HR
  - Dehydration
    - Loss of water from extracellular (intravascular and interstitial) and intracellular spaces (associated with ↑ serum Na^+ and osmolality)

- Edema
  - ↑ extracellular fluid volume (ECFV)
- Peripheral edema
  - Edema in a palpable area
- Anasarca
  - Severe, generalized edema

Abbreviations: BP, blood pressure; HR, heart rate

- Give the performance characteristics for detecting the likelihood of hypovolemia caused by blood loss (i.e. risk of serious amounts of blood loss).

  - ↑ pulse rate 30/minute or postural dizziness

	Sensitivity (%)	Specificity (%)
Moderate blood loss (450 – 630 mL)	22	98
Larger blood loss (630 – 1150 mL)	97	

	PLR	NLR
Urine specific gravity > 1.020	11	0.09
Dry axilla	2.8	0.6

  - Note
    - The finding of either postural dizziness (preventing measurement of vitals while standing) or a postural rise in the heart rate greater than 30 beats per minute is both sensitive (97%) and specific (98%), for large volume blood loss.
    - In patients with volume depletion due to vomiting, diarrhea, or decreased oral intake, few findings have proven to be useful.

Note: A postural increase in the pulse rate by > 30 bpm when moving from the supine to the standing position has a PLR < 2, as also does the finding of normal electrolytes and creatinine levels, or the fact that the patient who is pregnant. For this reason, these are not included here.

Abbreviations: CI, confidence interval; NLR, negative likelihood ratio; PLR, positive likelihood ratio

Adapted from: Simel, D.L., *et al*. *McGraw-Hill Medical* 2009, Table 24-8 and 24-9, page 327; Filate, W., *et al*. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, page 326.

SO YOU WANT TO BE A NEPHROLOGIST!

Differentiate hypovolemia (volume depletion) and dehydration.

- Hypovolemia: volume depletion is the loss of extracellular Na^+ from the GI tract or kidneys, leading to an increase in the serum urea nitrogen–to–creatinine, corrected by the rapid IV infusion of 0.9% "normal" saline to correct and associate hemodynamic instability
- Dehydration: the loss of intracellular water, leading to a rise in serum Na^+ and plasma osmolality, corrected by the slow IV infusion of 5% DW

(HE: Hypovolemia–Extracellular; DI: dehydration–intracellular)

- Perform a focused physical examination for dehydration.

➢ Postural changes

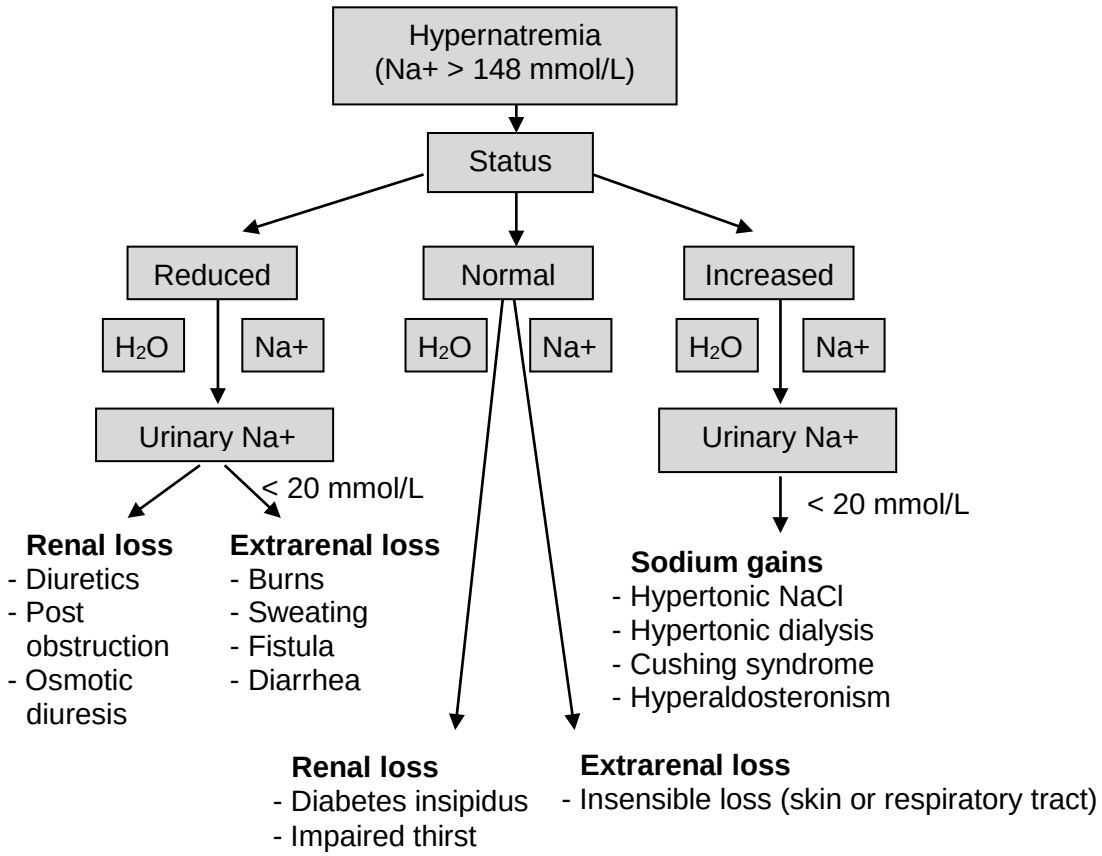
- HR increases by > 30 bpm after 1 minute of moving from a lying to a standing position
- BP falls by > 20 mm Hg after 1 minute of moving from a lying to a standing position

o CNS	- Confused - Weakness - Speech not clear or expressive
o Mouth	- Dry mucous membranes
o Eye and face	- Decreased eyeball pressure - Sunken eyes - "gaunt" face
o JVP	- Collapsed veins
o CVS	- Tachycardia - Postural hypotension
o Skin	- Reduced skin turgor (elasticity) especially arms, forehead, chest, abdomen - Dry axilla - Dry mucous membranes of mouth and nose - Longitudinal furrows on tongue
o Oliguria	- < 400 mL urine/24 hours

Total, body water in a male of 70 kg is about 40 L

Adapted from: Talley, N.J., *et al*. *Maclennan & Petty Pty Limited* 2003, Table 2.5, page 21 and McGee, S.R. *Saunders/Elsevier* 2007, Box 9-1, page 95.

Approach to Hypernatremia



Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 250.

➢ Clinical

- Take a directed history for the causes of lactic acidosis*

Mechanisms	Associations
○ ↑ Production	- Hypoxia - ↑ Skeletal muscle activity (i.e. status epilepticus or marathon runners) - ↑ Destruction of large tumour masses (i.e. lymphoma or leukemia) - Poisoning (i.e. CO or cyanide)
○ ↓ Transport	- ↓ Cardiac output

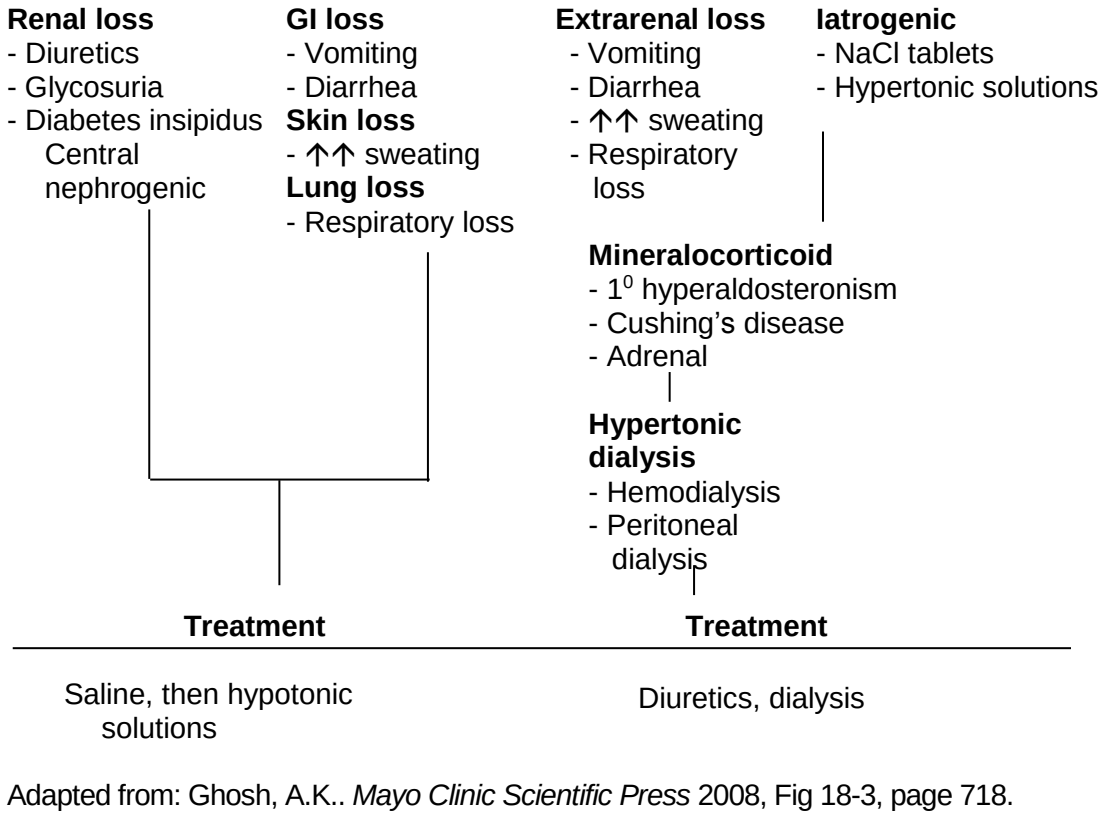
Mechanisms	Associations
○ ↓ Metabolism	- Liver failure - Liver hypoxia - Intoxication (phenformin or alcohol) - Diabetes mellitus
○ Miscellaneous	- Hemofiltration with lactate buffer - Pregnancy

➢ Types

- ○ Type A ↓ tissue perfusion and oxygenation
- ○ Type B No hypoperfusion or ↓ oxygenation
  - B1. Association with underlying disease
  - B2. Drugs and toxins
  - B3. Inborn errors of metabolism

Adapted from: Davey, P. *Wiley-Blackwell* 2006, Table 128.2, page 253.

- Take a directed history and perform a focused physical examination of hypernatremia.



Adapted from: Ghosh, A.K.. *Mayo Clinic Scientific Press* 2008, Fig 18-3, page 718.

HYPOKALEMIA

➢ Pathophysiology

- Give the causes of hypokalemia (K^+< 3.5 mmol/L).

Cause	Pathophysiological features
○ Primary or secondary glomerulopathy	○ ↑ Glomerular capillary permeability to protein
○ Tubular or interstitial disease	○ ↓ Tubular reabsorption of proteins in glomerular filtrate
○ Monoclonal gammopathy, leukemia	○ ↑ Production and overflow of low molecular weight proteins

Adapted from: Abuelo, J.G. *Ann Intern Med* 1983; 98:186-91.

- Give the causes of hypokalemia (K^+<3.5 mmol/L).
  - ○ ↓ Intake
    - Lack of K^+containing food in diet
    - Malabsorption- resins
  - ○ ↑ Gut loss
    - Vomiting
    - NG suction
    - Diarrhea
    - Fistulae
  - ○ ↑ Renal loss
    - Diabetes mellitus
    - K+ losing diuretics
    - Excess mineralocorticoid: steroids, Cushing's syndrome, Conn's tumor
    - Renal disease
      - ARF followed by diuretic
      - RTA
      - Fanconi's syndrome
      - Renal ischemia
  - ○ Shift
    - Familial periodic paralysis
    - IV insulin, glucose, HCO_3

Abbreviations: ARF, acute renal failure; IV, intravenous; NG, nasogastric tube; RTA, renal tubular acidosis

Adapted from: Burton, J.L. *Churchill Livingstone* 1971, page 109.

DISORDERS OF ACID–BASE BALANCE

- Definitions
  - Respiratory acidosis (low extracellular pH, high CO_2 content): any cause of hypoventilation
  - Respiratory alkalosis (high pH, low CO_2 content): any cause of hyperventilation
  - Metabolic acidosis (low pH, low CO_2 content)
  - Metabolic alkalosis (high pH, high CO_2 content
  - Mixed disorders, i.e. respiratory and metabolic acidosis in hypoventilated hypoxic patients; respiratory alkalosis and metabolic acidosis in salicylate poisoning

- Useful background

- Give the information required to evaluate the status of a patient with an acid–base disturbance:

  - Arterial blood gasses (ABG)
  - Plasma anion gap
  - Clinical evaluation of respiration
  - Normal ABG values

pH	7.35 – 7.45
pCO_2	35 – 45 mmHg
pO_2	80 – 100 mm Hg
HCO_3^-	22 – 26 mmol/L

Respiratory acidosis

- General idea: hypoventilation leads to accumulation of CO_2 from metabolism, which lowers the pH of body fluids

- Common causes
  - COPD
  - Drugs (narcotics, anesthetics)
  - Decreased LOC

- Normal compensation
  - The addition of bicarbonate raises the pH and buffers against respiratory acidosis.
    - Acute: bicarbonate increases 1 mmol/L for every 10 mm Hg increases in pCO_2
    - Chronic: the kidney forms new bicarbonate, resulting in a rise of 3 mmol/L for every 10 mm Hg increases in pCO_2

Respiratory alkalosis

- General concept: hyperventilation lowers pCO_2 and thereby raises pH of body fluids

- Common causes
  - Pneumonia
  - Pulmonary embolism
  - Sepsis
  - Pregnancy
  - Aspirin

- Normal compensation
  - Reduction in bicarbonate lowers the pH and buffers against respiratory alkalosis
  - Acute: bicarbonate decreases 1 mmol/L for every 10 mm Hg decrease in pCO_2
  - Chronic: the kidney excretes bicarbonate, resulting in a drop of 3 mmol/L for every mm Hg decrease in pCO_2

Metabolic acidosis

- General idea
  - ↓ ECF bicarbonate concentration →↓ pH
  - ↓ pH can be caused
    - Directly by the addition of H+ (which binds to bicarbonate)
    - Any other phenomenon which lowers the bicarbonate concentration
  - Use plasma anion gap to help determine etiology
  - Plasma anion gap (PAG)
    - PAG = Na+-(HCO_3 = Cl-)
    - Proportional to albumin concentration
    - Normal: 12 mmol/L when albumin is 40 g/L
    - If the compound that caused the acidosis contributes an anion, this will be in an increased PAG
    - In a pure anion gap acidosis, the drop in bicarbonate exactly matches in PAG
    - If the drop in bicarbonate is greater than the increase in PAG, it is either a non–-anion gap acidosis

➢ Causes

- Give the common causes of increased plasma anionic gap (PAG) metabolic acidosis (mnemonic KARMEL.).

  - **K**etoacidosis
  - **A**cetylsalicylic acid
  - **R**enal failure
  - **M**ethanol
  - **E**thylene glycol
  - **L**actic acidosis

- Give the common causes of non-PAG metabolic acidosis.

  - GI
    - Diarrhea
  - Kidney
    - Renal failure
    - Renal tubular acidosis
  - Endocrine
    - Mineralocorticoid deficiency
  - Hyperventilation
    - *Kussmaul breathing* should compensate for metabolic acidosis by ↓ the pCO_2 by the same amount as the ↓ bicarbonate

Metabolic alkalosis

➢ General idea
  - ↑ ECF bicarbonate → ↑ pH
  - ↑ pH caused initially by Na^+–H^+ exchange in the distal nephron
  - Then ↑ pH is perpetuated by proximal tubule reabsorbed bicarbonate

➢ Common causes:
  - ECF volume depletion
  - Diuretics
  - Vomiting
  - Excess mineralocorticoid activity

➢ Normal compensation
  - Hypoventilation should compensate for metabolic alkalosis by increasing the pCO_2 to a maximum of 50 mmHg

Adapted from: Filate, W., *et al*. *The Medical Society, Faculty of Medicine, University of Toronto* 2005, pages 330 and 331.

	Metabolic acidosis	Metabolic alkalosis
➢ Intake of acid or potential acid		
	o High protein or fat diet	- $NaHCO_3$
	o Rapid saline infusion	- Milk-alkali syndrome
	o ASA, $CaCl_2$, NH_4Cl	
➢ Production	o ↑ Catabolism	
	o Ketosis	
	o Lactic acidosis	
➢ Loss	o ↑ Loss of base	- ↑ Loss of acid
	- Diarrhea	▪ Vomiting
	- Fistula	▪ NE suction
	o ↓ Excretion of H^+	- ↑ Excretion of H^+
	- ARF, CRF, ARF/CRF	- Any cause of ↓ K^+
	- RTA	
	- Pyelonephritis	
	- Hydronephosis	
	- Carbonic anhydrase inhibitors	
	- Uretero–sigmoidoscopy	

Abbreviations: ARF, acute renal failure; CRF, chronic renal failure; RTA, renal tubular acidosis

POLYCYSTIC KIDNEY DISEASE

- Take a directed history and perform a focused physical examination for autosomal dominant polycystic kidney disease (ADPKD).

➢ Clinical

- o History
  - Back pain
  - Hematuria (also proteinuria)
  - Urinary tract infection
  - Hypertension–associated complications
  - Renal calculi
  - Cyst infection
  - Family history
  - Renal failure–associated complications
- o Physical examination
  - Signs of complications of hypertension, chronic renal failure

- Cyst
  - Liver
  - Pancreas
  - Ovary
  - CNS
- CNS
  - Cyst
  - Intracranial saccular aneurysm (berry aneurysm)
- CVS
  - Mitral prolapsed (20%)
  - Aortic valve abnormalities
- GI
  - Diverticulosis (colon)
  - Anterior abdominal wall hernias

Adapted from: Baliga, R.R. *Saunders/Elsevier* 2007, pages 322 and 323.

- Give the unilateral palpable kidney disease.

  - Congenital disease of a kidney
  - Bilateral renal disease, but the patient has had a nephrectomy
  - Polycystic kidney
  - Renal cyst
  - Renal carcinoma
  - Hydronephrosis
  - Hypertrophy of one functioning kidney after removal of the other

Source: Baliga, R.R. *Saunders/Elsevier* 2007, pages 329 and 330.

URINARY INCONTINENCE

➢ Risks

- Give the modifiable risk factors for urinary incontinence in adults.

  - Caffeine intake
  - Bowel problems (constipation, fecal impaction)
  - Fluid intake (1.5 – 2 L/day is considered appropriate)
  - Lower urinary tract conditions (urinary tract infection, urogenital atrophy)
  - Morbid obesity
  - Smoking
  - High–impact physical activities

- Medications
  - Diuretics
  - Anticholinergics
  - Cholinergic agonists
  - Alpha–agonists
  - Alpha–antagonists
  - Sympatholytic
  - Psychotropics
  - Alcohol
  - Sedative hypnotics
- Restricted mobility (includes dexterity in clothing removal, accessibility to toilets)

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, Canada: *Canadian Pharmacist Association* 2012, Table 1, page 875.

- For a detailed list of the causes of discolored urine, please see: Burton, J.L. Aids to Postgraduate Medicine. *Churchill Livingstone*, Edinburgh, 1971,

URINARY TRACT INFECTIONS (UTI)

- Definitions
  - Relapse
    - Recurrence with the same organism
  - Usually occurs within 4 weeks
  - Reinfection of a UTI
    - Recurrence with a different organism
  - Usually occurs > 2 weeks after treatment of the first UTI
- Pathogens
  - *Escherichia coli* 85%
  - *Staphylococcus saprophyticus* (coagulase–negative) 10%
  - Other gram–negative bacilli
    - *Proteus*
    - *Pseudomonas*
    - *Klebsiella*
    - *Enterobacter*
  - These “other” gram–negative bacilli are important for
    - Recurrent UTI
    - Complicated UTI (structural or functional urinary tract abnormalities)
  - Multiple pathogens, suspect:
    - Structural abnormalities
    - Contamination
  - *Candida* associated with
    - Diabetes
    - Catheters
    - Antibiotic users

- Diagnosis
  - Uncomplicated (normal lower and upper urinary tract)
  - Complicated
    - Structural or functional abnormalities (including catheters)
    - Extrremes of age
    - Diabetes
    - Multiple sclerosis (MS)
    - Spinal cord damage
    - HIV / AIDS
  - Urinalysis
    - Dipsticks
      - Leukocyte esterase and nitrate
    - Microscopy
      - Midstream urine, clean catch, unspun
      - > 10 WBC/mL (pyuria) → UTI
  - Urine culture
    - Dipsticks
    - ≥ 10^5 colony–forming units (CFU)/mL, collected as per urine microscopy, noted above
    - Obtain in
      - Pregnant women with asymptomatic bacteria
      - Complicated UTI (including suspected pyelonephritis)
      - Recurrent UTI
      - Possible resistant organism
      - Possible drug allergies
      - Before urological procedure

- Investigation

- Give the importance of knowing if UTI is likely to be “complicated”.
  - Requires diagnostic imaging (exclude intra–renal or peri–renal abscess
  - More likely to be multiple drug–resistant organisms

- Give the distinction between a relapse and a re–infection of an UTI.
  - Relapse within 2 weeks of therapy of UTI from original pathogen
  - Re–infection of UTI from a different pathogen

- Give the only two circumstances when it is appropriate to investigate for asymptomatic bacteriuria.
    - Patients who have had an invasive urological procedure
    - Pregnant women

➢ Prognosis
- Nosocomial UTI 2% – 4% develop bacteria
- This bacteria has mortality rate (MR) of 13%

Clinical Pearl

≥ 10^5 CFU/mL is diagnostic of UTI. Give the circumstances when lower CFU/mL is also diagnostic.

Acute dysuria, pyuria (> 10 WBC/mL), and 10^2 CFU/mL on urine cultures are diagnostic of UTI.

➢ Treatment
- Cystitis
    - Young women who are sexually active but not pregnant
    - Trimethoprim–sulfamethoxazole 160/800 mg *bid po* for 3 days
    - Nitrofurantoin 100 mg *bid po* for 5 days
    - Fosfomycin 3 g *po*, single dose
    - During pregnancy amoxicillin, or nitrofurantoin
- Recurrent UTI
    - > 25% in 1 month
    - Consider treatment for symptomatic infections
        - ≥ 2 in 6 months
        - ≥ 3 in 12 months
    - Radiological investigation
        - Suspected structural or functional abnormality
        - Renal calculi or UTI from *Proteus*
        - Multiple relapses (same strain)

- A 65 year–old man has fever, chills, low back pain, and a tender “bulky” prostate is palpable or digital rectal examination (DRE). Urinalysis shows pyuria and bacteruria. While waiting for the results of a “clean–catch” urine culture, give the empiric antibiotic choices for the 4 – 6 weeks treatment of the presumed prostatitis.
    - Timethoprim–sulfamethoxazole
    - Ciprofloxacin or levofloxacin

- Give the factors which increase a woman's risk of recurrent UTIs.

  - Pre–menopausal
    - UTI at age 15 or earlier
    - New sexual partner
    - Frequent sexual partner
    - Frequent sexual intercourse
    - Use of spermicidals
    - Vaginal colonization with uropathogens
    - Blood group ABO antigen non–secretor
    - Pelvic structural disorders
  - Post–menopausal
    - UTIs before menopause
    - Urinary incontinence
    - **Cystoide**
    - Postvoid residual urine
  - Prophylaxis
    - Dipsticks
    - Avoid use of spermicides
    - Cranberry juice trial (controversial)
    - Antibiotics
    - After intercourse
    - Continuous self–management
    - Intravaginal estrogen cream (post–menopausal)

Recurrent Postcoital UTI

A young sexually active woman suffers from recurrent postcoital urinary tract infections (UTI).

- Give the recommended therapy.

  - Avoid use of spermicidals
  - Postvoidal fluid intake to ↑ voiding
  - Antibiotic
    - Short course of ciprofloxacin
    - Maintenance antibiotic

CERVICITIS, URETHRITIS AND PROCTITIS

➢ Microbial causes

- Women
  - Cervicitis
    - *Chlamydia trachomatis*
    - *Neisseria gonorrhoeae*
- Men
  - Urethritis
    - *C. tachomatis*
    - *N. gonorrhoeae*
    - HSV
    - *Trichomonas vaginalis*
    - *Mycoplasma genitalium*
- Women and men
  - Proctitis
    - *C. trachomatis*
    - *N. gonorrhoeae*
    - HSV
    - Syphilis

➢ Clinical

- Cervicitis
- Urethritis
  - Dysuria
  - Purulent discharge from penis
- Proctitis
  - Pain and tenesmus
  - Rectal discharge

➢ Treatment

- Give the reason why the treatment of urethritis and cervicitis is usually with the following recommended antibiotic regimen.
  - Azithromycin or cefoxitin, most common organism is *Neisseria gonorrhoeae*
  - Cefoxitin for penicillinase–producing *N. gonorrhoeae*
  - Ceftriaxone for commonly associated *Chlamydia trachomatis*

ACUTE PYELONEPHRITIS

- Definition
  - "….an inflammation of the renal parenchyma typically resulting from an ascending bladder infection". (MKSAP 16, Infectious disease 2012, page 31)

- Approach
  - Outpatient
    - May chose to begin with loading dose ciprofloxacin 400 mg IV
    - Ciprofloxacin 500 mg *bid po* for 7 days
    - If resistance to fluoroquinolones > 10%, use ceftriaxone 1 g IV, followed by *po* fluoroquinolones
    - Other options aminoglycoside or β–lactam
  - Inpatient
    - Choice depends on local resistances
    - IV fluoroquinolone, but not moxifloxacin
    - Aminoglycoside + ampicillin
    - Cephalosporin (extended–spectrum)
    - Penicilin (extended–spectrum) + aminoglycoside
    - Carbapenem

GENITO–URINARY CANCER

To be covered here

- Prostate
- Testicle
- Bladder
- Kidney

"Hard work and good intentions are admirable, but for the successes of life, you have to put the puck in the net."
Grandad

Renal Cancer

- Give the role of targeted therapy against 3 tumors, using pharmaceutical treatment against vascular endothelial growth factors (VEGF), tyrosine kinase inhibitors (TKI), or epidermal growth factor receptor (EGFR).

Tumor	VEGF–MA	VEGF–TKI	EGFR–MA	EGFR–TKI
Brain	+			
Head and neck			+	
Lung	+		+	+
Breast	+			
Ovary	+			
Liver (HCC)		+		
Pancreas				+
Colon	+		+	
GIST		+		
Renal		+		
CML				+

Abbreviations: CML, chronic myeloid leukemia; EGFR, epidermal growth factor receptor; GIST, gastrointestinal stroma tumor; MA, monoclonal antibody; TKI, tyrosine kinase inhibitor

- Types
  - Cortex
    - Clear–cell most common
    - Papillary 15% (better prognosis)
    - Chromophobe 10%
  - Non–pelvis
    - Transitional cell
- Risk factors
  - Genetic
    - vHL (von Hippel–Lindau syndrome)
  - Lifestyle
    - Smoking
    - Obesity
    - Occupational exposure
  - Dialysis
    - Renal cysts
- Diagnosis
  - Ultrasound
    - Simple cysts — Benign
    - Complex cysts } Malignant
    - Mass }

- Treatment
  - < 4 cm partial nephrectomy
  - > 4 cm radical nephrectomy
  - Metastases
    - Nephrectomy plus interferon alpha
    - ↑ vascular endothelial growth factor (VEGF) as in HLG: sorafenib, sunitinib, bevacizumab
    - mTOR inhibitors: temsirolimus, everolimus
    - Surveillance at risk–adjusted intervals

- Metastatic renal cancer is treated with immunotherapy using interferon alpha. Even when the patient has no local symptoms, give the additional therapy that is indicated.

  - Nephrectomy
    - "renal cancer is the only malignancy in which removing the primary tumor in the setting of metastatic disease, an improve overall outcome, rather than just reduce local symptoms" (MKSAP 16, Hematology and Oncology 2012, page 198)

- Give the type or name of targeted therapy against malignant kidney tumor.

	Therapies
o TKI	o Sorafenib, or sunitinib
o EGFR–TKI	o Imatinib, or gefitinib
o EGFR–MA	

- Give the treatments of renal cancer which cause renal dysfunction.

  - Renal tubules
    - Cisplatin
    - Methotrexate
    - Radiation
  - Bladder
    - Hemorrhage cystitis
      - Cyclophosphamide
      - Ifosfamide
      - Radiation

Note: nephrectomy is a treatment for renal cancer, and dose renal function, so would be an allowable answer!

Prostate Cancer

- Predisposing causes
  - ↑ age
  - Prostatitis
  - Family history
  - High dose vitamin E intake (i.e. for treatment of fatty liver)

- Clinical
  - Obstructive symptoms
  - Recent erectile dysfunction (ED) from cancer invasion of neurovascular bundle
  - Bone pain (metastases)
  - Spinal cord compression

- Diagnosis
  - ↑ prostate specific antigen (PSA); > 20 ng/mL)
  - Abnormal digital rectal examination (DRE)
  - Transrectal ultrasound (TRUS)
  - Endorectal MRI
  - Transrectal biopsy, multiple core samples
  - Bone scan and CT for high risk disease (T3, T4; ↑ PSA; Gleason score of 8 to 10)

- Treatment
  - Use nomograms to help make appropriate therapeutic decisions, i.e. www.ncca.org/professionals/physician_gls/PDF/prostate.pdf
  - Nomogram recommendations are based on TNM, PSA, Gleason score, and life expectancy
  - Basic concept of treatment choices

Risk	Life Expectancy (years)	Therapy choices
Low	< 10	- Wait and watch
	≥ 20	- Radiation therapy, or - Intensity–modulated external beam, or - Brachytherapy, or - Radical prostatectomy, nerve–sparing
High*	< 5	- Androgen deprivation therapy (ADT); surgical and chemical castration - SC or IM gonadotropin–releasing hormone (GnRH) agonists or antagonists plus anti–androgens *po*

Risk	Life Expectancy (years)	Therapy choices
	≥ 5	- Radiation therapy, or - ADT followed by: ▪ Radiation therapy, or ▪ Radical prostatectomy

*When prostate cancer is considered high risk disease: T3 /T4; PSA > 20 ng/mL; Gleason score of 8 to 10.

- Hormone refractory or metastatic prostate cancer

Docetaxel plus prednisone

↓ Non–response

Cabazitaxel
or
Sipuleucel–T (autologous cellular immunotherapy)

Testicular Cancer

- Types
  - Germ–cell tumors
    - Seminonas
    - Non–semimonas
      - Embryosomal
      - Choriocarcinoma
      - Yolk sac
      - Teratoma
      - Mixed

- Risk factors
  - Family history
  - Cryptorchidism
  - Klinefelter syndrome

TRIVIAL TIPS

In patient with cryptorchidism, testicular cancer may develop in either the undescended or in the normal descended testicle.

- Clinical
  - Mass
  - Pain
  - Metastases
  - Gynecomastia

- Give the pathophysiology of gynecomastia in Klinefelter's patient with testicular cancer.
  - While Klinefelter syndrome itself predisposes the patient to have testicular cancer, gynecomastia arises from the ↑ human chorionic gonadotropin (HCG) from the tumor

- Laboratory

- Give the interpretation of abnormal concentrations of 3 serum tumor markers of testicular cancer.
  - ↑ HCG suggests testicular tumor
  - ↑ lactate dehydrogenase (LDH) → rapid turnover of malignant cells
  - ↑ alpha–fetoprotein (AFP) → the testicular tumor is a non–seminoma
  - HCG, LDH and AFP are used with the TNM stage to determine the final stage of the tumor
  - Measure these 3 tumor markers *q* 2 months for 1 year to detect recurrence, then yearly for 10 years

- Give the tumor markers for seminomatous and non–seminomatous testicular tumors.

  - Seminoma - ↑ beta–human chorionic gonadotropin (β–HCG)
  - Non–seminoma - ↑ alpha fetoprotein (AFP)

- Treatment
  - Radical orchiectomy, plus post–surgical treatment:
  - Seminoma
    - Stage I
      - Active follow–up, or
      - Radiation of para–aortic nodes, or
      - Carboplatin
      - Relapse → chemotherapy (multiple agents)
    - Stage II
      - Radiation, or
      - Platinum–based chemotherapy +/- bleomycin

- Non–seminoma
  - Poorer prognosis requiring more aggressive therapy
  - Ia
    - Active follow–up
  - Ib
    - Active surveillance, or
      Retroperitoneal lymph node dissection (RPLND),
      Platinum, etoposide and bleomycin
  - More advanced
    - RPLND, or
    - Platinum–based chemotherapy
- Note:
  - Testicular tumors may contain more than one component
  - If one component is non–seminomatous, based on either histopathology or tumor marker, it is treated as a non–seminoma

Bladder Cancer

- Risks
  - Smoking
  - Occupational exposure
  - Risk of field cancerization effect, ↑ risk of developing transitional cell cancer of the renal pelvis

- Diagnosis
  - MRI
  - Intravenous pyelogram (IVP)
  - Cystoscopy and biopsy
  - Cytological studies of urine
  - TNM staging

- Treatment
  - Non–invasive
    - Transurethral resection of the bladder tumor (TURBT)
    - Intravesicular agents
      - Low risk
        - Mitomycin, or
        - Gemcitabine
      - High risk
        - Bacillus Calmette–Guerin (BCG) for 1 year
  - Follow-up
    - Cystoscopy
      - *q* 3 months for 2 years, then
      - *q* 6 months for 2 years, then
      - Annually
  - Metastatic disease
    - Platinum–based chemotherapy
    - Palliation

Cervical Cancer

- Incidence
  - Marked ↓ with
    - Screening (Pap smear)
    - Prevention of human papilloma virus (HPV)

- Risk factors
  - Early sexual activity
  - Multiple sexual partners
  - Sexually transmitted disease (STDs)
  - Multiparity
  - Oral contraceptive pill (OCP), long–term use
  - Smoking

- Diagnosis
  - Pelvic examination
  - Colposcopy
  - Biopsy

- Treatment
  - Excisional cone biopsy
  - Radiation
  - Hysterectomy
  - Cisplatin–based chemotherapy
  - Post–operative radiation plus chemotherapy

- Follow–up after treatment
  - Pap smear *q* 3 – 6 months for 2 years, then *q* 6 months for 3 years, then *q* 1 year
  - Recurrence
    - After surgery
      - "salvage" radiation plus chemotherapy
    - After radiation
      - Pelvic exenteration
    - Distant or unresectable
      - Palliative chemotherapy
      - Supportive or palliative care

- Give the surgically identifiable factors in patient with cervical cancer, which indicate the need for post–surgical adjuvant chemotherapy.

  - Large tumor
  - Invasion deeply
    - Into the stroma
    - Into the lymphovasculature
  - Positive lymph nodes

INDEX

Note: Page number followed by f and t indicates figure and table, respectively.

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INFECTIOUS DISEASES

BITES AND SCRATCHES

Animal Bites

- Causes and associations
  - Bacteroides
  - *Bartonella henselae* (Cat scratch disease)
  - *Capnocytophaga*
  - *Pasteurella multocida*
  - *Porphyromonas*
  - *Prevotella*
  - *Staphylococci*
  - *Streptococci*
- Special clinical points
  - Depth of injury and risk of involving joints and bone
  - Immune status (of patient)
  - Previous immunization
    - Tetanus
    - Rabies
- Treatment (including prophylaxis)
  - No penicillin allergy
    - Mild
      - 5 days of amoxicillin–clavulanate
    - Severe
      - IV cefoxitin, or carbapenem
  - Penicillin allergy
    - Mild
      - Fluoroquinolone, or
      - Doxycyclin, or
      - Trimethoprim–sulfamethoxazole plus clindamycin
    - Severe
      - Fluoroquinolone plus clindamycin
      - Vancomycin
  - Suspected MRSA
    - Vancomycin
  - Duration
    - Skin: 2 weeks
    - Joints: 4 weeks
    - Bones: 6 weeks

Cat Scratch Disease

- Cause
  - *Bartonella henselae*
- Clinical
  - 2 days to 2 weeks after cat scratch or bite
    - Erythema
    - Pustule
    - Papule
  - 2 to 3 weeks
    - Lymphadenopathy
    - Tender
    - Suppurative
- Treatment
  - Self–limited
  - If infected, azithromycin, short–term
  - If not infected, consider prophylaxis with azithromycin

Human Bites

- Give the organism which might infect the person exposed to a human bite.

  - Anyone who sustains a human bite wound, including a clenched–fist injury, is at risk of developing an infection from the bacterial flora of the mouth, and should be treated properly. These organisms include:
    - α–hemolytic *Streptococcus*
    - *Staphylococcus*
    - *Haemophilus*
    - Eikenella corrodens
    - β–lactamase producing anaerobes

- Causes and associations
  - Oral flora
    - GABHS
    - *Staphylococcus*
    - *Haemophilis*
    - *Eikenella corrodens*
  - Other infections in blood of attacker
    - HBV
    - HCV
    - HIV
    - HSV
    - Syphilis
- Closed–fist punch
  - Access for possible involvement of the joints, tender bone

Abbreviation: GABHS, group A β–hemolytic *Streptococcus*

➢ Treatment

In person who is tolerant to penicillin, amoxicillin–clavulanate is recommended.

- Give the treatment of choice for patient with wounds who is allergic to penicillin.
    - Clindamycin plus moxifloxacin is recommended
    - No evidence of infection
        - Prophylaxis: amoxicillin–clavulanate, 5 days
    - Evidence of infection
        - Cefoxitin or carbopenem
    - MRSA
        - Vancomycin

SKIN AND SOFT TISSUE INFECTION (SSTI)

➢ Types
- Usually
    - Group A β–hemolytic *Streptococci* (GABHS)
    - *Staphylococcus*
- Abscess
- Draining wound
- Forms of skin and soft tissue infection (SSTI)
    - Erysipelas
        - Infection of upper dermis
        - Legs, arms, face
    - Cellulitis
        - Infection of lower dermis, and subcutaneous fat
    - Abscess
        - I and D (incision and drainage)
        - Empiric antibiotics
        - Lymphangitis
        - “Peau d’orange”
    - Blood cultures from erysipelas, cellulitis are positive in only ~5%

Please see standard textbooks or reviews such as UptoDate or MKSAP 16, Infectious disease 2012, Table 10, page 13; for cellulitis pathogens with specific behaviours / risk factors

Purulent Cellulitis

- Give the recommended treatment for non–purulent cellulitis in patient with fever and leukocytosis, and the likely organisms against each treatment.
  - Likely organisms
    - β–hemolytic *streptococci*
    - Community–associated methicillin–resistant Staphylococcus aureus (CA–MRSA)
  - Recommended antibiotic
    - Clindamycin

➢ Differential

- Give the non–infectious conditions which mimic infectious cellulitis.
  - Familial Mediterranean fever (FMF)
    - Erysipelas–like, usually unilateral lesion on lower leg or foot
  - Erythromelalgia
    - Redness of extremities
      - Warm burning
      - Paroxysmal
  - Sweet's syndrome
    - Acute febrile neutrophilic dermatitis
    - Usually affects
      - Middle–aged women
      - Papules / plaques
      - Tender
    - Site
      - Upper extremities
      - Neck
      - Upper trunk

- Give the empiric therapy for purulent cellulitis.
  - The following suggested antibiotic choices are for community–associated methicillin–resistant *Staphylococcus aureus* (CA–MRSA):
    - Trimethroprim–sulfamethoxazole
    - Doxycycline
    - Clindamycin
    - Linezolid

Staphylococcus aureus

- Pathophysiology
  - Genes encoding for cytotoxins
    - Destroy WBC
    - Cause tissue necrosis

- Clinical
  - Common presentations
    - Purulent SSTIs
    - Pneumonia

- Treatment (empiric antibiotics)

- Give the empiric antibodies recommended for MRSA diagnosed in outpatient (community) or hospital (nosocominal) setting.
  - In an outpatient setting
    - Trimethoprim–sulfamethoxazole
    - Tetracycline
    - Linezolid
    - Clindamycin
      - Monitor clindamycin resistance in your area of practice, and do not use empirically for MRSA in resistance > 10%
  - In a hospital setting
    - Linezolid (also covers β–hemolytic streptococci)
    - Vancomycin
    - Ceftaroline
    - Telavancin

Necrotizing Fasciitis

- Definition: “necrotizing fasciitis is a skin and soft tissue infection (SSTI) that extends beyond the epidermis, dermis and subcutaneous fat tissue to the fascia and potentially, to the underlying muscle”

- Types
  - Type I - Polymicrobial
  - Type II - Monomicrobial

- Diagnosis
  - High index of clinical suspicion
  - MRI

A patient with compensated cirrhosis from iron overload presents with hemorrhagic bullae and sepsis after cutting his fat on a sharp stick while swimming in the ocean of Mexico. Necrotizing fasciitis is diagnosed.

- Give the likely causative organism.
  - The likely causative organism is *Vibrio vulnificus*, to which the patient is more prone because of the cirrhosis and the excess iron.

- Treatment
  - Emergent (MR ~ 50%)
  - Surgical debridement, respected daily, as indicated
  - Empiric antibiotics

SO YOU WANT TO BE AN INFECTIOUS DISEASE EXPERT!

- Give the molecular **mechanism** for the development of methicillin–resistant *Staphylococcus aureus*, and explain why ceftaroline is effective against MRSA.
  - *Staphylococcus aureus* organisms acquire the gene MUC
  - MUC encodes for the membrane penicillin–binding protein 2a
  - This penicillin–binding protein 2a in the membrane of *S. aureus* has a low affinity of β–lactam agents
  - Ceftaroline is a fifth–generation cephalosporin which has high affinity for penicillin–binding protein 2, and thus, effective against MRSA.

Abbreviations: CSF, cerebrospinal fluid; UTI, urinary tract infection

- Give the organisms causing type I and type II necrotizing fasciitis, and the recommended empiric antibiotics.

Organisms

Type I (polymicrobial)	Type II (monomicrobial)
○ *Staphylococci* ○ *Streptococci* ○ Aerobic gram–negative bacilli ○ Anaerobes - *Clostridium* - *Bacteroides* - *Peptostreptococcus*	○ *Streptococcus pyogenes* ○ *S. agalactiae* ○ *Vibrio vulnificus* ○ *S. aureus* ○ *Clostridium perfringens*

Necrotizing fasciitis due to *Streptococci* develop toxic shock syndrome (TSS) (please see the next subsection) in 50%

- Type I
  - Vancomycin, linezolid, or daptomycin, plus
  - Piperacillin–tazobactam ("pip-tazo"), or
  - Metronidazole plus cefepime, or
  - Meropenem, or imepenem
- Type II (monomicrobial, GABHS or clostridium)
  - Penicillin plus clindamycin

Note: Use of IV–immunoglobulin (IV–IG) is controversial, and generally used if TSS has developed or if there is "a high risk of death" (remember that the overall mortality rate for necrotizing fasciitis is 30 – 70%)

MCQ Alert

There are unique presentations for *V. vulnificus* that makes it a "must" for a multiple choice question (MCQ).

- Gram–negative rod
- Common in coastal waters of Mexico
  - Break in skin, swimming
- High risk for
  - Immunocompromised
  - Hemosiderosis and hemochromatosis
- Associated pain is severe and out of proportion to skin changes

Toxic Shock Syndrome (TSS)

- Definition
  - Shock syndrome, exfoliating rash, "packing" infected by *Staphylococcus aureus* and group A β–hemolytic *streptococci*
- Causes and associations
  - Toxin–producing *Staphylococcus* and *Streptococci*
  - May be associated with necrotizing fasciitis

- Give the conditions associated with the development of TSS.
  - Menstruation, especially with the use of tampons
  - Infections
    - Surgery or blunt trauma
    - Childbirth
    - Nose
      - Sinus infection with nose packing
    - Skin
    - Bone
    - Pnemonia
    - Influenza
    - Varicella

    } for TSS from *Streptococcus*

    o "packing"
    - Tampon for menstrual bleeding
    - Nasal packing
    - Wound packing
    - Abscess
  - Medication
    - NSAIDs (for TSS from Streptococcus)
  - Injections
    - IV drug use (IVDU)

- Clinical
  - The body temperature is often > 38.9°C (102.0 F, and systolic blood pressure < 90 mm Hg
  - Localizing signs are not necessarily present
  - Diagnostic criteria have been established for TSS, depending upon whether the causative organism is Staphylococcal (*S. pyogenes* or B–hemolytic *Streptococcus* [GABHS])

- Prophylaxis (for secondary transmission of GABHS - TSS)
  - Penicillin-based prophylaxis
  - Contact isolation until 24 hours after first day of empiric antibiotics completed
    - In index patient
    - Close contacts
    - Others
      - Household contacts
      - Diabetics
      - CV disease
      - Cancer
      - IVDU
      - Infection
        - HIV
        - Varicella
      - Users of corticosteroids

- Treatment
  - Toxic shock syndrome
  - Empiric
    - Carbapenem or penicllin, plus
    - β–lactamase inhibitor, plus
    - Clinidamycin
  - IV immunoglobulin
  - Once organism is found, give clindamycin plus nafcillin

Note: do **not** use corticosteroids

"Use diagnostic imaging to guide your clinical impression, not to make the diagnosis."

Dr. Joel Hurwitz

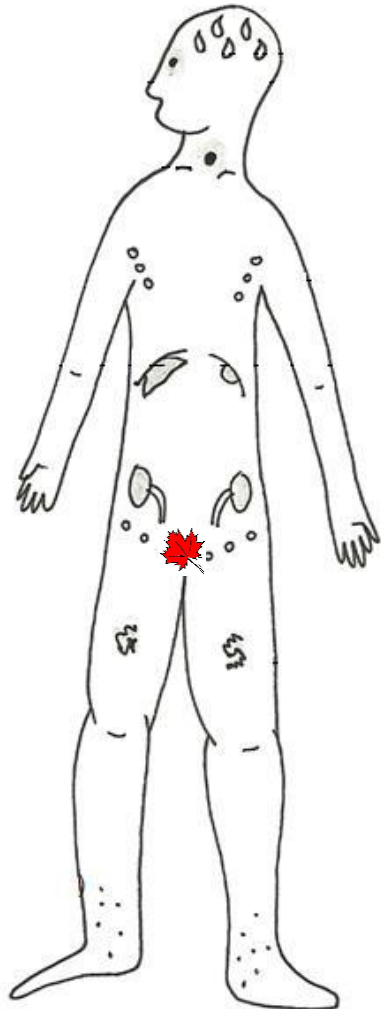
VIRAL INFECTIONS

Epstein–Barr Virus (EBV)

Jaundice

Sore throat

Abnormal LEs (90%)



Fever

CNS
Encephalitis
Myelitis

eneralized
lymphadenopathy

omegaly (in 50%)
hrombocytopenia
lemolytic anemia
old agglutinin

lgia

ulopapular rash with
npicillin (common)

- EBV infection may be associated with cancer in certain populations
  - Nasopharyngeal cancer (Chinese)
  - Burkitt's lymphoma (African)
  - Post transplant lymphoproliferative disorder (PTLD)

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 298.

- Clinical
  - EBV infection is usually associated with infectious mononucleosis syndrome (IMS) (flu–like illness, fever, posterior cervical lymphoadenopathy, asplenomegaly, sore throat, measles–like rashes after ampicillin, atypical peripheral blood lymphocytes and positive serology).
  - Some patients may have atypical presentations.

- Give the presentations of EBV infection other than the typical IMS or EBV-associated malignancies.
  - CNS - Aseptic meningitis
    - Aseptic encephalitis
  - Liver - Hepatitis
  - Blood - Hemolytic anemia
    - Thrombocytopenia

- Give the viruses which are associated with infectious mononucleosis syndrome (IMS).
  - CMV
  - EBV
  - HIV

➢ Complications

- Give the malignant or premalignant conditions associated with EBV.
  - Lymphoma - B–cell
    - T–cell
    - Hodgkin's
    - Post–transplantation lymphoproliferative disorder (PTLD)
  - Leukoplakia, oral hairy - Painless, white, corrugated plaques on edge of tongue
  - Nasopharyngeal carcinoma

➢ Diagnosis

- Give the serological tests for the present and past EBV infection.

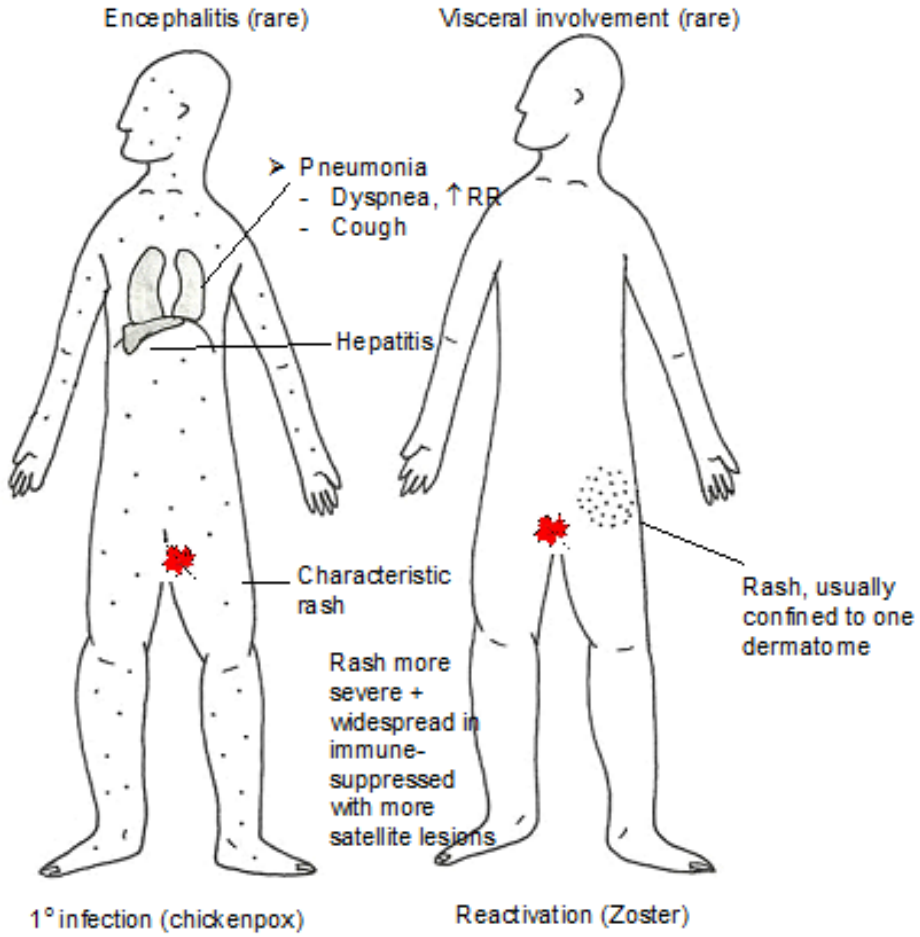
	EBV Infection	
	Present acute primary	Past
Viral capsid antigen IgM	↑	0
Early antigen IgE	↑	0
Epstein–Barr nuclear antigen-1 IgE	↓ / 0	↑

Note; Viral capsid antigen (VCA) IgG is increased in both, hence, does not help to distinguish between present and past EBV infection

- Treatment
  - Conservative
  - No anti–viral drugs
  - Corticosteroids for severe
    - Lung disease
    - Hemolytic anemia

Varicella–Zoster Virus (VZV) **Infections**

- Clinical

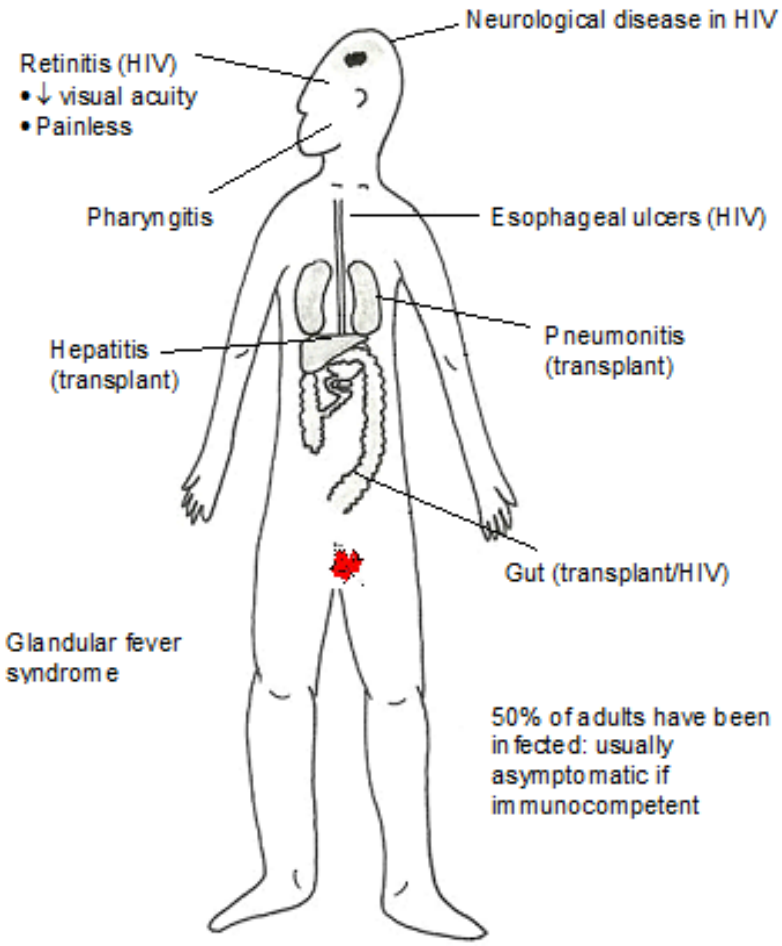


Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 298.

- Chickenpox
  - Varicella vaccine
  - Varicella zoster immune globulin (VZIB)
  - Varicella zoster immune globulin (VariZIG) product
- Shingles
  - Vaccine for > age 60 years
    - Antivirals
    - Acyclovir
    - Valacyclovir
    - Famciclovir

Cytomegalovirus (CMV)

- Clinical



Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 298.

➢ Treatment

- Give the treatment of choice to be given within 4 days (96 hours) to pregnant or immunocompromised patients who are exposed to varicella.
    - VariZIG
    - Immune globulin IV
    - Do not give varicella vaccine
        - Live virus is usually contraindicated in immunosuppressed patients

VIRAL HEMORRHAGIC FEVERS (VHF)

➢ Causes and associations
    - RNA viruses, including Yellow fever, Dengue fever, Embola hemorrhagic fever
    - Potential of person–to–person transmission

➢ Clinical
    - Widespread vascular damage, i.e.:
        - Petechial hemorrhages
        - Conjunctival injection
        - Hypotension

➢ Diagnosis (specialized diagnosis)
    - Detect viral protein antigens
    - IgM antibodies
    - PCR
    - Culture

➢ Treatment
    - Supportive care

Ebola

➢ Microbiology
    - Ebola virus (EV) is a filoviridae with a lipid envelop genome base 10 kb, and icosahedral–shaped organism causing a febrile illness in the setting of a multi–system disease.

- Some of the filamentous virions fuse end–to–end, resulting in a “bowl of spaghetti” appearance.
- EV may survive for weeks at room temperature in dry blood.
- Ebola virus is a biosafety level 4 pathogen because of its high (~50%) mortality rate.

➢ Clinical

- Infection in the mononuclear phagocytic system leads to widespread cellular necrosis including cerebral necrosis of glial with infarction, interstitial pneumonitis, hepatitis, skin rashes and bleeding from any mucosal surface, such as the GI tract.
- The role of possible aerosol infectivity is controversial.

➢ Laboratory

- Viremia is detected by ELISA and RT-PCR is commonly positive, with IgG and IgM autoantibodies developing in survivors.

➢ Treatment

- There is no preventive vaccine, or proven anti–viral drug.
- Pharmaceuticals studied in non–human primates, i.e. an adenovirus–vectored glycoprotein gene, are being rushed to human use in the recent West African epidemic.
- Treatment is confined to isolation, hydration, nutrition, and public health measures to prevent epidemicization.

For the following “**Buzzwords**”, give the likely pathogen of infection.

Buzzwords used in MCQ	Implications
○ Atypical lymphocytes, heterophile antibody positive	EBV
○ Bell’s palsy syndrome	HSV
○ Bulbar palsy plus flaccid paralysis, or “Five Ds”	Botulism
○ Conjunctival suffusion	*Leptospira interrogans*
○ Deep bone culture	Osteomyelitis
○ Jarisch–Herxheimer reaction	*T. pallidum* (syphilis)

Buzzwords used in MCQ	Implications
○ Non–tender, red macules on palms and soles	Infectious endocarditis (Janeway lesion)
○ Oral hairy leukoplakia	HIV
○ Painless, pruritic papule with black eschar, plus wide mediastinum on chest X–ray	Anthrax
○ Papules and vesicles all at the same stage, beginning in the face	Smallpox
○ Progressive multifocal leukoencephalopathy (PML)	Polyomavirus JC
○ Pneumothorax in HIV infected person	*Pneumocystis jiroveci*
○ Whitlow	HSV
○ West Africa, worldwide epidemic	Ebola virus

TICK-BORNE DISEASES

To be covered here:

- ○ Lyme disease
- ○ Babesiosis
- ○ Southern Tick–Associated Rash Illness (STARI)
- ○ Ehrlichiosis and Anaplasmosis
- ○ Rocky Mountain Spotted Fever (RMSF)

- Give the tick–borne pathogens treated with doxycycline.

  - ○ Lyme disease
    - *Borrelia burgdorferi*
  - ○ Human granulocytic anaplasmosis
    - *Anaplasma phagocytophilum*
  - ○ Rocky Mountain spotted fever (RMSF)
    - *Rickettsia rickettsii*

Lyme Disease

- Causes and associations
  - Vector deer tick
    - *Ixodes scapularis*
  - Causative spirochete
  - Note
    - May be associated with co–infection with *Babesia micoti*, causing Babesiosis

- Clinical

1 – 2 weeks

- Tick attachment → Early localized (EM, erythema migrans) → Spirochetemia → Early disseminated → Late
  - When a patient presents with skin rashes from an endemic area of Lyme disease, only about half will remember tick attachment, and the initial skin lesion may be erythema migrans (EM).
  - It is important to recognize early localized Lyme disease to treat the tick–borne disease early and to prevent later serious complications.

- Describe the typical **erythema migrans** (EM) of Lyme disease.
  - An expansile, target–like skin lesion often associated with a tick bite or attachment causing Lyme disease or Southern tick–associated rash illness.
  - Centre
    - Clear (looks like a “bulls-eye”)
    - May become necrotic or vesicular
  - Edges
    - May become confluent macule
  - Associated cellulitis
  - EM may spread to the skin sites distant from the initial attachment

- What is the empiric treatment for erythema migrans?
  - It is not necessary to distinguish between which tick-borne infection is causing the EM.
  - Begin treatment for EM with doxycycline

- Name the infectious cause of EM mimicking Lyme disease but occurs in the Southern USA.
  - Southern tick–associated rash illness (STARI)
  - Early–disseminated disease
    - Incubation period, 3 to 6 weeks
    - Febrile illness, with lymphadenopathy
    - Heart
      - Myocarditis (5%)
      - Heart block
    - CNS
      - CN palsy, unilateral or bilateral
      - Aseptic meningitis
      - Radiculopathy
  - Late–stage disease (60%)
    - Incubation period, months to years
    - Joints
      - Migratory, mono– or oligoarticular arthritis
      - Knee induced in 85%
      - Remission and recurrences in years later
    - CNS
      - Encephalopathy
      - Encephalitis

➢ Post–Lyme Disease Syndrome
  - "….patients with confirmed Lyme disease based on clinical and laboratory criteria who have persistent with constitutional symptoms despite appropriate antibiotic treatment"
  - Supportive treatment only

➢ Testing
  - Do not test an asymptomatic person after a tick bite
  - "….restricted primarily to patients with clinically suggestive signs or symptoms (other than erythema migrans) who reside in or have travelled to an endemic area" (MKSAP 16, Infectious disease 2012, page 26)

- Diagnosis
  - Blood is positive or equivocal for ELISA test for antibody to *B. burgdorferi*, followed by:
    - Confirmatory Western blotting
  - If only 1 or more of symptoms and signs (other than EM) **IgM antibody**
    - The finding of *B. burgdorferi* antibodies in patients who have non–specific symptoms of fatigue or myalgia or who are unlikely to have been exposed to a water tick, likely presents a false–positive test results for Lyme disease, hence, be treated.

Lies about Lyme Disease

- "Early Lyme disease is diagnosed with serology testing."
  - "No": serology testing may be negative for early Lyme disease
    - The earliest sign of Lyme disease is "erythema migrans" (large red rings on the skin)
- Be satisfied that "treatment for Lyme disease is satisfsctory when the titre of antibody falls."
  - "No": serology testing is not a reliable gauge for adequacy of treatment.
- The treatment of choice for *Borrelia burgdorferi* infection is amoxicillin."
  Not quite a "lie"
  - Empiric treatment
    - Amoxicillin
    - Cefuroxime
    - Doxycycline
  - Lyme–associated carditis or CNS disease
    - Ceftriaxone
  - Arthritis or facial palsy
    - Doxycycline
- "The treatment for Lyme disease in pregnancy is – Doxycycline" ???
  - No-No-No!
    - "lie, BIG BAD LIE": doxycycline should **not** be given in pregnancy

➢ Treatment

- Give the treatment for the patient with Lyme disease caused by *Borrelia burgdorferi*, who develops bradycardia (Lyme myocarditis).

○ 1st degree heart block (HB), asymptomatic	- Out–patient cefuroxime, or doxycycline *po*
○ 2nd or 3rd degree HB	- In–patient monitoring - IV ceftriaxone

Babesiosis

➢ Causes and associations
- ○ Directly, from tick–borne protozoal infection with *Babesia microti*
- ○ Transfusion with infected blood

➢ Clinical
- ○ Organism replicates in RBCs, and may be
- ○ Asymptomatic, or progress to affect:
- ○ Blood
  - Hemolysis
  - DIC
- ○ Kidney
- ○ Heart
  - HF
- ○ Multi-organ failure

Abbreviations: AKI, acute kidney injury; DIC, disseminated intravascular coagulation; HF, heart failure

➢ Diagnosis
- ○ PCR of blood for *B. microti*
- ○ RBC, thin
  - Ring forms of *B. microti* in RBCs
  - Do not confuse with *Malaria falciparum*
- ○ For symptoms, or asymptomatic parasitemia > 3 months

- Treatment
  - Mild
    - Atovaquone plus azithromycin or quinine and clindamycin
  - Severe
    - Atovaquone plus quinine and clindamycin
    - Exchange transfusion

Southern Tick–Associated Rash Illness (STARI)

- Southern USA
- EM in early stage
- Vector of the tick, *Ambylomma americanum*; causative agent unknown
- Does not progress
- Treat with doxycycline 100 mg *bid po* for 1 – 2 weeks (again, do **not** use in pregnancy)

Ehrlichiosis and Anaplasmosis

- Causes and associations
  - Tick–borne disease
  - HE
    - Human granulocyte Ehrlichiosis
      - Lone–star tick SE, mid–Atlantic USA
  - HGA
    - Human granulocyte anaplasmosis
      - Deer tick NE, NC USA
- Clinical
  - Ferile illness
  - Usually no skin, but when present
    - Maculopapular
    - Petechial
  - Meningoencephalitis in < 20%
- Laboratory
  - Blood
    - Abnormal liver enzymes (LEs)
    - Lymphopenia, thrombocytopenia
    - Buffy coat, clusters of bacteria in WBCs
  - CSF
    - Pleocytosis, lymphocytic
    - ↑ protein

- Treatment
  - Doxycycline 100 mg *bid po* for 7 – 14 days (caution: do not use in pregnancy)
    - Treat early to ↓ mortality rate (MR)

Rocky Mountain–Spotted Fever (RMSF)

- Causes and associations
  - Tick–borne rickettsial disease
  - Rickettsia riskettsii
- Clinical
  - Fever
  - GI symptoms
  - Skin rash
    - Early 15%
    - Late 90%
    - Macules
    - No blanching
    - Wrists, ankles → petechial everywhere except on the face
- Laboratory
  - Abnormal liver enzymes (LEs)
  - Thrombocytopenia
  - No lymphopenia or leukopenia (as in HME or HGA)
  - Serological testing
    - Positive, or
    - Seroconversion on convalescent serum
  - Skin biopsy
    - Positive for *R. rickettsii*
- Treatment
  - Doxycycline 100 mg *po* for 1 – 2 weeks

HIV / AIDS

- Definition
  - CD4 count < 200/mL
  - AIDS–indicating opportunistic
    - Infections
    - Malignancies

- Diagnosis
  - Two–stage serological testing (may be negative in AS [acute retroviral infection])
  - Repeat testing of positive enzyme immunoassay (EIA) by Western blotting
  - Performance characteristics
  - Sensitivity 99.5%
  - Specificity 99.99%
  - When EIA is positive but Western blot negative
  - False–positive EIA
  - Indeterminate Western blot on repeat testing cross–reacting antibody due to infection
  - Quantitative polymerase chain reaction (RNA–PCR)
- Clinical
  - One of the major indications for HAART / ART therapy in patient with HIV infection is history of an AIDS–defining illness (opportunistic infection or malignancy).

- Give the **AIDS–defining illnesses**.

- Site
  - CNS
    - HIV
    - Encephalopathy
    - Toxoplamosis
    - Lymphoma (primary)
    - Progressive multiple leukoencephalopathy
  - Eye
    - CMV–retinitis
  - Lung
    - Candidiasis of esophagus
    - HSV of esophagus
    - HIV–wasting syndrome
    - Chronic
      - Cyptosporidiosis
      - Isosoporiasis
  - GU
    - Cervical cancer (invasive)
- Organism
  - Extrapulmonary
    - Coccidioidomycosis
    - Cryptococcosis
    - Histoplasmosis
- Tumors
  - Kaposi sarcoma

- Lymphoma
  - Burkitt's
  - Immunoblastic
- *Mycobacterium tuberculosis*
- Extrapulmonary
  - *Mycobaterium avium* complex (MAC)
  - *Mycobacterium kansasii* (MK)
- *Pneumocystis*
- *Salmonella* bacteremia, recurrent
- CMV infection other than LSLN (liver, spleen, lymph nodes)

Adapted from: MKSAP 16, Infectious disease 2012, Table 54, page 92.

SO YOU WANT TO BE AN ID CONSULTANT!

- In patient with HIV/AIDs, what is **eosinophilic folliculitis**?
  - An infection of hair follicles, typically papular, pruritic and seen in HIV–infected patients.

Clinical Alert

Primary prophylaxis is recommended in HIV / AIDS when the CD4 count is < 200/μL for *Pneumocystis jiroveci*, < 100/ml and positive serology for toxoplasmosis, < 50 μL for *Mycobacterium avium* complex (MAC), and tuberculin skin test (TST) > 5 mm or positive interferon γ release assay (IGRA) for tuberculosis.

- Give the precaution necessary before therapy with TMP–SMX, azithromycin, and INH (isoniazid).
  - Exclude acute infection with MAC (blood cultures) on TB to ↓ development of resistance and use of inadequate drug doses.

Clinical Gem

Beware the “company” that diseases keep.

In patient with oral hairy leukoplakia, and an EBV infection, give the other viral infection which must be excluded.

- Oral hairy leukoplakia is very highly suggestive of an infection with HIV.

➢ Screening

- Give the criteria inscreening for HIV infection.
  - The answer may vary by country policy.
    - For USA, the Centers for Disease Control and Preventions (CDC) ”....recommend HIV screening for all individuals between the age of 13 and 64 years at least once and--- these with risk factors [should] undergo annual testing”. (MKSAP 16, Infectious disease 2012, page 181)

➢ Prophylaxis

- Pre–exposure: emtricitabine or tenofovir
  - HIV (-ive) person having sexual activity with HIV (+ive) person
- Post–exposure early use of drugs after exposure
  - Occupational, and possibly sexual
- Perinatal screening
  - Anti–retroviral therapy (ART) to ↓ risk of transmission to fetus

➢ Treatment

- Give the current guidelines for anti–retroviral (ART, HAART) treatment for HIV infection.
  - Symptoms of HIV infection (please see above)
  - CD4 ≤ 500/μL
  - AIDS–deficiency illness (opportunistic infection or malignancy)
  - HIV–nephropathy
  - Co–infection, HBV / HCV
  - Pregnancy and HIV infection (HAART reduces HIV transmission from 25% → 2%

- Standard preferred starting regimen (may be modified by sensitivity testing)
  - 2 nucleoside RTIs (tenofovir plus emtricitabine), plus
  - 1 non–nucleoside RTI (efavirenz), or
  - 1 potease–inhibitor
  - Atazanavir or darunavir, plus
  - Small dose of ritonavir
  - Other regimens used in pregnancy: lamivudine and zidovudine, plus
  - Lopinavir or ritonavir (protease–inhibitors)

Abbreviation: RTI, reverse transcriptase–inhibitor

- Give the adverse effects and complications of **HAART therapy**.
  - HAART (antiviral therapy with highly active antiviral therapy) is associated with:

Metabolic disorders	- Lipids ▪ ↓ total HDL, LDH cholesterol concentrations ▪ ↑ serum triglyceride - Lipodystrophy - Insulin resistance ▪ ↑ fasting glucose ▪ ↑ Hb A1C - Metabolic lactic acidosis
Bone	- ↑ osteopenia - ↑ osteoporosis
Kidney	- HIV–nephropathy
Liver	- ↑ risk of co–infection with HBV / HCV - ↑ risk of progression to cirrhosis (HIV plus HCV)
CVS	- ↑ atherosclerosis - ↑ cardiac deaths
Immune reconstitution inflammatory syndrome (IRIS)	- Reconstitution of the immune system which occurs in weeks to months after starting HAART results in a marked inflammatory response, especially against TB and fungal infections

- Opportunistic Infections:

CD4 cell count per µL	Organism / Infection
> 200	- Candidiasis
< 200	- *Pneumocystis jiroveci*
< 100	- *Cryptococcus*
< 50	- *Toxoplasma gondii* - CMV - MAC *(Mycobacterium avium*) - TB - Poxvirus *Molluscum contagiosum* - Bortonella bacillary angiomatosis - HHV–8 Kaposi sarcoma caused by human herpes virus

CASE CHALLENGE

A pregnant woman, who has no–HIV–associated symptoms form her infection, showed normal CD4 count and a low viral load. From her reading, she does not require HAART, and she is concerned about the teratogenicity of the HAART drugs such as efaviranz.

- Give your advice about the treatment for HIV infection during **pregnancy**.
  - There are criteria to follow before starting HAART for HIV infection
  - However, all HIV–infected pregnant woman should be treated to prevent transmission of HIV to the fetus (25% → 2%)
  - While efavirenz is contraindicated in pregnancy, other regimens are safe.
  - She reads treatment with regimen such as lamivudine plus zidovudine and lopinavir–ritonavir

- In patient with suboptimally controlled HIV with RNA viral loads despite usual appropriate HAART therapy, why does **resistance testing** is performed while the patient remains on HAART?
  - A drug "holiday" (stopping HAART) would only lead to ↑ HIV load
  - "resistance testing done while the patient is not receiving [HAART] therapy may be unreliable without the selective pressure of the medications to maintain the presence of mutations in the predominant [resistant] viral population" (MKSAP 16, Infectious disease 2012, page 170)

Acute Retroviral Syndrome (ARS)

- Fibrile illness 2–4 weeks after exposure
- High viral loads due to early lack of immune response
- HIV testing still negative in the window interval, until seroconversion occurs
- Not yet clear whether ART (antiviral therapy) is beneficial for ARS

Chronic HIV Infection

- HIV infects CD4 T–lymphocytes which replicate and integrated into the genome of the host cells, and cause immune compromise
- Non–opportunistic infections become more:
  - Common
  - Severe
  - Prolonged
- Examples include:
- Mouth - Herpes simplex virus (HSV) infection
- Lung - Pneumococcal pneumonia
- GU - Vaginal candidiasis recurrent or refractory
  - Herpes zoster infection (HZV)
  - Genital HSV infection

➢ Clinical

- Give the common clinical features of chronic HIV infection.

- Systemic
  - Fever
  - Night sweats
  - Fatigue
  - ↓ weight
- Mouth
  - Aphthous ulcers
  - Hairy leukoplakia
  - Gingivitis
  - Peri–odontitis
- Skin
  - Seborrheic dermatitis
  - Psoriasis
  - Tinea
  - Onychomycosis

- GI - Diarrhea
- GU - Nephropathy
- CNS / PNS - Peripheral neuropathy
- Blood - Cytopenia

Adapted from: MKSAP 16, Infectious disease 2012, Table 50, page 87.

SEXUALLY TRANSMITTED DISEASES

- For an excellent background on how to take a directed history for sexually transmitted disease (STD), see: Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, pages 89 and 90.

- Give the sexually transmitted pathogens and diseases each cause.
  - *Chlamydia trachomatis* (chlamydia)
  - Hepatitis B and C (hepatitis)
  - Herpes simplex virus (HSV; herpes)
  - Human Immunodeficiency Virus (HIV/AIDS)
  - Human papilloma virus (genital warts)
  - *Neisseria gonorrhoeae* (gonorrhea)
  - *Trepomena pallidum* (syphilis)

Source: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, page 90.

- Cervicitis, urethritis - *Chlamydia trachomatis*
  Proctitis, Eididymitis - *Neissera gonorrhoeae*

- Genital ulcers
  - HSV infection
  - Syphilis
  - Chancroid
  - Lymphogranuloma venereum

- Genital warts - Condylomata acuminanta (HPV)

- Give the **complications** of sexually transmitted diseases **in women.**
  - Acute salpingitis
  - Pelvic inflammatory disease
  - Infertility
  - Ectopic pregnancies
  - Arthritis
  - Conjunctivitis
  - Urethritis
  - Fitz–Hugh–Curtis syndrome (GC or chlamydial infection of the liver capsule)

Source: Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, pages 90 and 91.

Chlamydia trachomatis

- Demography
  - < 25 years
  - Sex
    - Unprotected
    - Multiple partners
    - New partners
- Clinical
  - Cervicitis
  - Urethritis
  - Proctitis
- Complications in women
  - Infertility
  - Pelvic inflammatory disease (PID)
  - Ectopic pregnancy
- Diagnosis
  - Discharged swab / urine
    - Culture
    - Nucleic acid amplification (NAA) testing
  - Screen
    - Sexually active women ≤ 25 years
    - Other high risk factors
  - Check sexual partners
    - From time of symptom
      - All sex partners in last 60 days
      - Last sex partner if > 60 days

- Treatment
  - Ceftriaxone, 250 mg IM, one dose
  - Plus Azithromycin, 1 g *po*, one dose,
  - Or Cefixime, 400 mg *po*, one dose
  - Plus Doxycycline 100 mg *po bid* for 7 days

Note: High rate of co–infection with *N. gonorrhoeae*

Pelvic Inflammatory Disease (PID)

- Definition
  - A polymicrobial infection (usually *C. trachomatis* plus *N. gonorrhoeae*) arising from infection ascending from the cervix, to cause
    - Endometritis
    - Salpingitis (or salpingitis plus endometritis)
    - Tubo–ovarian abscess
    - Scarring of fallopian tube (infertility)
- Diagnosis
  - High index of suspicion in sexually active young women, especially with fever, cervicitis discharge, tenderness of uterus and adenexia
- Treatment
  - Mostly as outpatients, unless PID is complicated
    - Pregnant
    - Proven or suspected tubo–ovarian abscess
    - Failure of outpatient therapy
    - Systemic toxicity
    - Possible surgical emergency

      po / IM
      - Ceftriaxone, 250 mg, one dose, plus
      - Doxycycline, 100 mg, *po bid* for 14 days, plus /
    - Metronidazole, 500 mg *po bid* for 14 days
    - IV
      - Cefotetan, 2 g *q* 12 h, or
      - Cefoxitin, 2 g *q* 6 h, plus
      - Doxycycline, 100 mg IV *q* 12 h

- Give the recommended antibiotic therapy that covers the likely causes of the polymicorbial infection in patient with cervicitis, with or without PID.
  - Without PID
    - Ceftriaxone IM, **XI,** plus azithromycin *po*
  - With PID
    - *Neisseria gonorrhoeae*
    - *Chlamydia trachomatis*
    - Aerobes
    - Anaerobes
  - Antibiotic combinations
    - For no systemic toxicity: ceftriaxone IM **IX,** plus doxycycline *po* for 14 days
    - With systemic toxicity: clindamycin IM
  - Note: Men who have had sexual contact with women who has PID need to be evaluated and treated for infection with the organisms noted above.

Epididymitis

- Demography
  - < 35 years
    - *C. trachomatis* or *N. gonorrhoeae*
  - Older man ± benign prostatic hypertrophy (BPH)
    - Enteric gram–negative organisms
  - Men who have sex with men (MSM), "insertive" partner in anal intercourse
    - Enterobacteriaceae
- Clinical
  - Unilateral pain or tenderness of epididymis and testis
  - Enlarged and tender spermatic cord
  - Urine
    - WBC ≥ 10/hpf
    - Positive dipstick leukocyte esterase
  - Note
    - Differentiated from testicular torsion
- Treatment
  - Ceftriaxone, 250 mg IM, one dose, plus
  - Doxycycline, 100 mg *bid* for 10 days

Note: With regard to treatment of cervicitis, urethritis, PID, epididymitis, please refer to standard medical textbooks or to reviews such as MKSAP 16, Infectious disease 2012, Table 26, page 45.

Genital Ulcers

- Clinical
  - HSV–1 primary infection
    - Skin
    - Vesicles → pustules → ulcers on red base and linear ulcers
  - GU
    - Women cervicitis
    - Women and men urethritis
  - Nodes
    - Inguinal lymphadenopathy, tender
  - HSV–2
    - Recurrent genital and perianal ulcers
    - Subclinical viral shedding is common, with transmission genital ulcers is less common
- Diagnosis
  - Serological testing
  - Culture
  - Molecular tests, i.e. PCR
- Treatment
  - Primary infection (usually HSV–1)
  - Recurrent infection, including continued suppressive therapy for > 6 recurrences per year

Please see standard testbook or recent review such as UptoDate or MKSAP 16, Infectious disease 2012, Table 27, page 46.

Syphilis

- Clinical

- Give the **stages of syphilis** infection.
  - Primary
    - Single or multiple round indurated painless chancre with raised border appearing in area of sexual contact
    - Genital lesions may be associated with non–tender lymphadenopathy

- Secondary
  - Non–pruritic macular, papular or pustular rash on palms and soles
  - On mucosal surface
  - Silvery erosions with red border
- Tertiary
  - Involvement of CNS (meningovascular, parenchyma), eye, CVS (aortitis)

- Give the differences between early and late latent syphilis.
  - Asymptomatic (latent), plus serology positive
    - ≤ 1 year – early
    - > 1 year – late or latent, syphilis of unknown origin

➢ Treatment

- Primary, secondary, early latent
  - Benzathine penicillin G, 2.4 million units IM, one dose, or
  - Doxycycline, 100 mg *po bid* for 14 days
- Late latent
  - Benzathine penicillin G, 3-4 milllion units IM *q* w for 3 weeks, or
  - Doxycycline, 100 mg *po bid* for 28 days
- Neurosyphilis
  - Aqueous crystaliine peniclillin G, 3-4 million units IV *q* 4 hours for 10-14 days
  - 18-24 million units IV continuous infusion, per day for 10 – 14 days

Please see a standard textbook or recent review UptoDate or MKSAP 16, Infectious disease 2012, Table 28, page 47.

CLINICAL CHALLENGE

- Give the clinical features of **Jarish–Herxheimer reaction**.
  - Antibiotic kills the syphilitic spirochetes within 2 hours after releasing an endotoxin.
  - The endotoxin causes fever, myalgia, headache, skin rash and hypotension.
  - The patient is treated sytomatically, and the antibiotic is continued if necessary.
  - Curiously, Jarish-Herxheimer reaction is more common during pregnancy.

Chancroid

- Causes and associations
  - *C. trachomatis*
- Clinical
  - Papules and perianal painless ulcers
  - Proctocolitis
  - Painful unilateral inguinal lymphadenopathy
  - Suppuration, drainage
- Diagnosis
  - NAA testing, including PCR
- Treatment
  - Doxycycline, 100 mg *po bid* for 21 day, or
  - Erythromycin, 500 mg *qid* for 21 day

The Three Musketeers plus d'Artagnan

- For a mucopurulent urethral discharge in male or cervicitis in female, give the 4 most likely pathogens which may be part of co-infection.
  - *Neisseria gonorrhoeae*
  - *Chlamydia*
  - HIV
  - Syphilis
- Give the most likely pathogens for genital ulcers.
  - Chancroid (*Haemophilus ducreyi*)
  - Herpes simplex virus 1 or 2 (HSV)
  - Llymphogranuloma venereum (LGV) caused by *C. trachomatis*
  - Syphilis (*T. palladum*)

Vaginitis

- Give the commonest causes of vaginitis.
  - Infectious
    - Candidiasis
    - *N. gonorrhoeae*
    - *Chlamydia trachomatis*
  - Non–infectious
    - Coitus
    - Allergic reaction to substances placed in the vagina
    - Post–menopausal atrophy

- Give conditions associated with HSV infection.
  - Genital herpes
  - HIV (HSV → ↑ transmission rate of HIV)
  - Benign recurrent lymphocytic meningitis
  - Recurrent erythema multiforme (EM)

"Thought is the wind, knowledge is the sail,
and mankind is the vessel."

Augustus Hare

"When the world says, "Give up", Hope
whispers, "Try one more time."

Anonymous

FEVER OF UNKNOWN ORIGIN (FUO)

- Definition: "….an illness that lasts at least 3 weeks in patient with temperature greater than 38 °C (101.0 °F) on several occasions and whose diagnosis remains uncertain despite having been evaluated in hospital for at least 1 week".

  MKSAP 16, Infectious disease 2012, page 52.

- Type

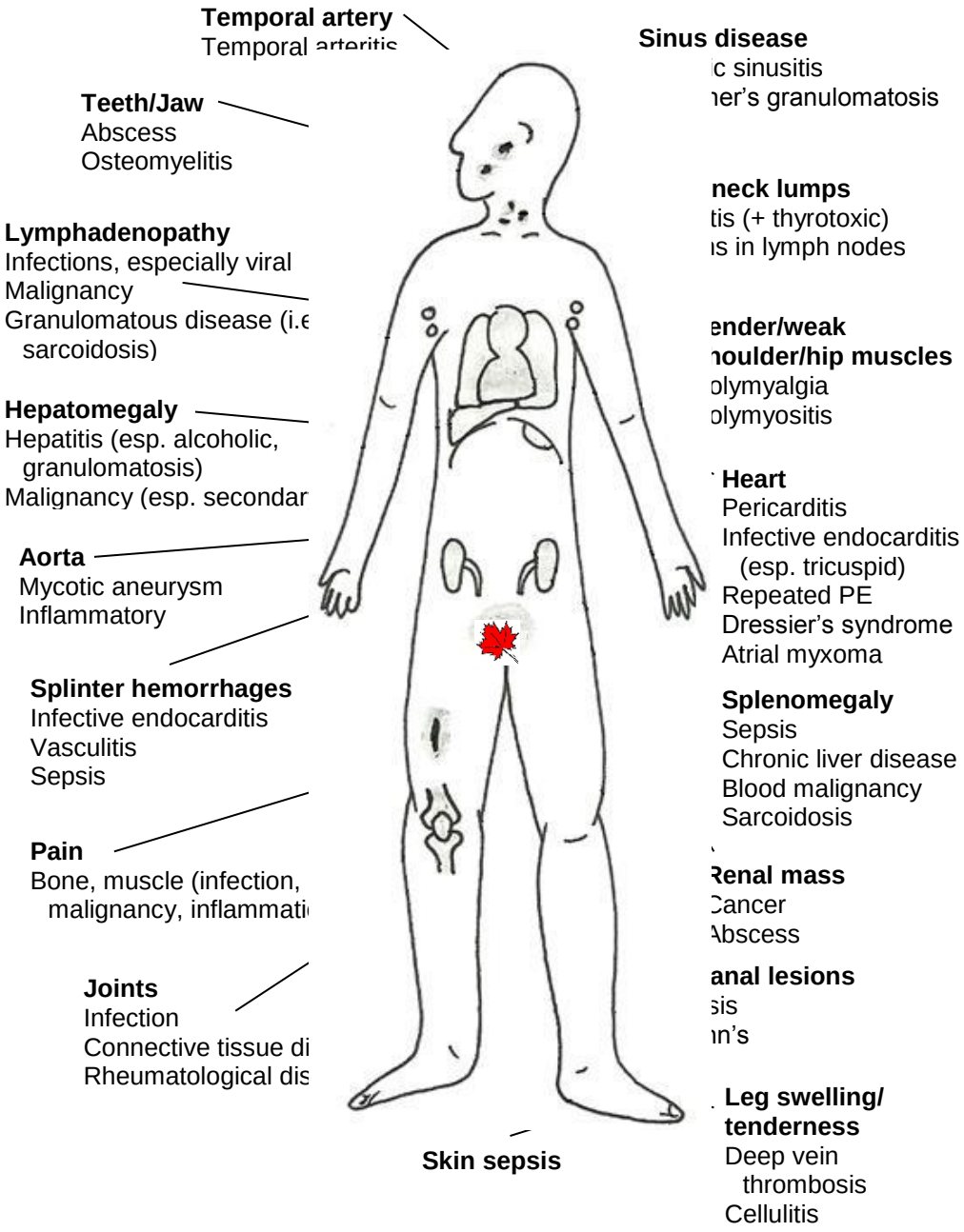
Type of FUO	Temperature °C (°F)	Duration	Diagnosis remains uncertain
○ Classic	> 38.3 (101.0)	> 3 wk	> 1 week hospital investigation
○ Modified classic	> 38.0 (100.4)	> 3 wk	> 3 days hospital investigation, or > 2 outpatient visits with tests not showing cause
○ Health–care associated	> 38.0 (100.4)	> 3 days	Hospitalized patient Acute care Infection not present (or incubating on admission)
○ Immune–deficient	> 38.0 (100.4))	-	> 3 days appropriate (includes 2 days for incubation of cultures)
○ HIV (confirmed) – related	> 38.0 (100.4))	> 3 weeks outpatients, or > 3 days in patients	

SO YOU WANT TO BE AN INFECTIOUS DISEASE EXPERT!

- Give the types of **hereditary periodic fever syndrome** in which there is > 14 days without fever between recurrent episodes of FUO.
  - Hyperimmunoglobulin D syndrome (HIDS)
    - Autosomal recessive
    - Clinical
      - Lymphadenopathy
      - Abdomen
        - Pain
        - Diarrhea
      - Joints
        - Pain
      - Skin
        - Maculopapular rash
      - Serum
        - ↑ IgA, ↑ IgD
  - Tumor–necrosis factor receptor–1 associated periodic syndrome (TRAPS)
    - Autosomal dominant
    - Clinical
      - Eyes
        - Periorbital edema
        - Conjunctivitis
      - Abdomen
        - Pain
      - Joints
        - Arthritis
      - Skin
        - Red patches
      - Testes
        - Pain
  - Muckle-Wells syndrome
    - Autosomal dominant
    - Clinical
      - Ears ↓ sensoneural hearing
      - Abdomen pain
      - Joints arthralgia or arthritis
      - Skin urticarial
      - Amyloidosis
  - Familial Mediterranean fever (FMF)
    - Autosomal recessive
    - Clinical
      - Chest
        - Pain
      - Abdomen
        - Pain
      - Joints
        - Arthritis
      - Serositis
      - Skin
        - Foot rash

➢ Clinical

- Perform a focused physical examination for fever of unknown origin (FUO).



Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 70.

- Give the common causes of fever of unknown origin.
  - Infections
    - Most common cause; common illnesses presenting in atypical manner
    - Most common infectious causes
      - Lung
        - Tuberculosis
      - Heart
        - Infective endocarditis
      - GI and GU
        - Abdominal and pelvic abscess
    - Infection (extensive search in HIV infections) EBV, CMV, HBV, HCV
  - Neoplasms (infiltration)
    - Lymphoma
    - Solid tumors (gastrointestinal tract, liver, renal cell, sarcoma)
    - Leukemia, and other hematological tumors
    - Atrial myxoma
    - Inflammatory: IBD, connective tissue diseases
    - Vascular: pulmonary emboli (PE)
    - Iatrogenic: drug–induced (malignant hypertrophy)
    - Congenital: familial Mediterranean fever (FMF)
  - Connective tissue disease (autoimmune)
    - Temporal arteritis and polymyalgia rheumatic
    - Polyarteritis nodosa
    - Systemic lupus erythematosus (SLE)
    - Still disease
    - Iatrogenic (drugs, toxin)
  - Special considerations
    - Heart
      - Endocarditis
      - HACEK
        - *Haemophilus aphrophilus*
        - *Actinobacillus actinomycetemcomitans*
        - *Cardiobacterium hominis*
        - *Eikenella corrodens*
        - *Kingella* species
    - Blood
      - Lymphoproliferative disorders
      - Hematoma
    - Lung
      - Pulmonary embolus (PE)
      - TB

  - Endocrine
    - Hypo–/ hyperthyroidism
    - Pheochromocytoma
  - Factitious
  - Habitual hyperthermia
  - Hereditary periodic fever syndromes
  - Ideopathic (50%)

Adapted from: Jugovic, P.J., *et al*. *Saunders/ Elsevier* 2004, pages 37 to 39.

Bacteremia in febrile patients

Risk Factors	PLR	NLR
o Renal failure	4.6	0.8
o Hospitalization due to trauma	3.0	NS
o Intravenous drug use	2.9	NS
o Previous stroke	2.8	NS
o Poor functional performance	3.6	0.6
o Rapid fatal disease (< 1 month)	2.7	NS

Abbreviation: NLR, negative likelihood ratio; PLR positive likelihood ratio

- Note: Some clinical features are not included above because the PLR are < 2 which include age 50 years or more and diabetes mellitus.

Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 16-2, page 180.

- Give the conditions in patient with fever of unknown origin where **a bone marrow aspiration** may be useful in the diagnosis.
  - Malignancy
    - Leukemia
    - Lymphoma
    - Bone cancer
  - Infection
    - TB
    - Malaria
    - Kala–azar
    - Brucellosis

- Take a directed history and perform a focused physical examination for **post–operative (post-op) fever**.
  - Post–operative risk factors and complications
    - Age > 50 years
    - Pre–existing cognitive dysfunction
    - Depression perioperative derangements
    - > 5 prescribed medications post–operatively
    - Use of anti–cholinergics pre–operatively
    - Cardiopulmonary bypass
    - ICU setting
  - Wound
    - Inflammation and leakage
  - IV site
    - Cellulitis
  - Limbs
    - Thrombophlebitis
  - Medications and blood products
    - Medications (both previous and new)
    - Blood product reactions
    - Allergies
  - Lung
    - Atelectasis
    - Aspiration
    - Pneumonia
    - Pulmonary embolus
  - GI
    - Ileus
      - Perforation
      - Abscess
  - UTI

Adapted from: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, pages 76 to 78.

The presence of **skin rash** in patients **with fever** helps to narrow the likely conditions causing the fever.

- Give the causes of fever and skin rash.
  - Vesiculobullous
    - Herpes viruses (particularly varicella zoster virus)
    - Coxsackie
    - *Enterovirus*
    - *Mycoplasma*

○ Petechia, purpura or skin hemorrhage	- Meningococcal septicemia - *Staphylococcus aureus* - Viral hemorrhagic fevers - Typhus - Leptospirosis - Gram–negative septicemia
○ Nodular rash	- Erythema nodosum
○ Diffuse generalized erythema	- Scalded skin syndrome - Toxic shock syndrome (TSS) ▪ Usually due to staphylococcal colonization of tampons ▪ Symptoms during or shortly after menstruation ▪ Fever, hypotension, shock ▪ Scarlet skin eruption ▪ Desquamation ▪ Multi–organ failure
○ Maculo-papular rashes (non-specific)	- Drug reaction - Infection - Self–limiting viral infections - HIV seroconversion - Dengue fever

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 72.

- Give the performance characteristics for patients with fever.

Physical examinations	PLR	NLR
○ Urinary catheter	2.4	NS
○ Central venous line	2.0	NS

Abbreviation: NLR, negative likelihood ratio; PLR positive likelihood ratio

Note: Numerous findings are not listed here, because their PLR is < 2.

- ○ These include:
  - Temperature ≥ 38.5 ^{o}C
  - Tachycardia
  - Respiratory rate > 20/minute
  - Hypotension
  - Acute abdomen
  - Confusion
  - Depressed sensorium

Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 16-2, page 180.

- Give the performance characteristics of the prognosis of clinical findings in fever > 39 °C.

Findings	PLR	NLR
○ Temperature > 39 °C		
○ Predicting hospital mortality in patients with pontine hemorrhage	23.7	0.4
○ Hypothermia		
- Predicting hospital mortality		
▪ From pump failure in patients with heart failure	6.7	NS
▪ In patients with pneumonia	3.5	NS
▪ In patients with bacteremia	3.3	NS

Abbreviation: NLR, negative likelihood ratio; NS, not significant; PLR positive likelihood ratio

Adapted from: McGee, S.R. *Saunders/Elsevier* 2007, Box 16-3, page 182.

SEPTIC SHOCK

➢ Definition: "….an exaggerated inflammatory response to an infectious stimulus characterized by severe catabolic reaction, widespread endothelial dysfunction, and release of inflammation agents" (MKSAP 16 2013, Pulmonary, page 82)

○ Systemic inflammatory response syndrome (SIRS) includes
- ↑ temperature (T)
- ↑ heart rate (HR)
- ↑ respiratory rate (RR)
- ↓ neutropenia (WBC)

○ Sepsis is SIRS with suspected infection
- 20% for each sepsis–induced dysfunction
- 17% due to inappropriate antibiotic are used

- Define fever of unknown origin (FUO), sepsis and systemic inflammatory response syndrome (SIRS).

Responses to infection	Endpoints to define sepsis or SIRS
↑, ↓ T	> 38.0 °C (100.4 °F), or < 36.0 °C (96.8 °F)
↑ HR	> 90 bpm
↑ RR	> 20/minute, or a PCO_2 < 32 mmHg
↑ WBC	> 12,000/μL, or < 4000/μL plus 10% bands
○ Sepsis	- Known or suspected infection (positive cultures not necessary), plus ≥ 2 criteria above
○ Systemic inflammatory response syndrome (SIRS)	≥ 2 criteria above - Severe sepsis ▪ Sepsis–induced hypotension / hypoperfusion - Septic shock ▪ Sepsis–induced hyotension / hypoperfusion despite appropriate resuscitation with fluids

"Let's see if there is a mechanistic information that we can tease out."

Grandad

"Be a leader, an icon for your profession"

"Let your actions speak for your competence"

"Live life larger to live life longer"

Anonymous

➢ Pathophysiology

- Give the changes in cardiac output (CO), pulmonary capillary wedge pressure (PCWP) and systemic vascular resistance (SVR) in 4 shock syndromes.

Shock syndrome	CO	PCWP	SVR	Associations
○ Cardiogenic	↓	↑	↑	Signs of heart failure (HF)
○ Hypovolemic	↓	↓	↑	Signs of blood loss / volume loss
○ Obstructive	↓	↓	↑	Pulmonary embolism (PE) Tension pneumothorax Cardiac tamponade
○ Anaphylactic	↑	N	↓	Skin Rash Urticaria Angioedema Lung Wheeze Stridor
○ Septic*	↑ /↓		↓	↑ T, ↑ HR, ↑ RR, ↓ $aPCo_2$, ↑ / ↓ WBC

*Early ↑ and then ↓ CO

Abbreviations: HR, heart rate; T, temperature; WBC, white blood cells

➢ Clinical

○ Pulse rate (PR) and fever (PR normally increases 8 bpm for each 1 °C increase in body temperature)
- Lower pulse than expected for temperature
  - Typhoid fever
  - Brucellosis
  - Meningitis
- Higher pulse than expected for temp'
  - Polyarteritis (in fact, fever may be only slight)
    - Fever with purpura

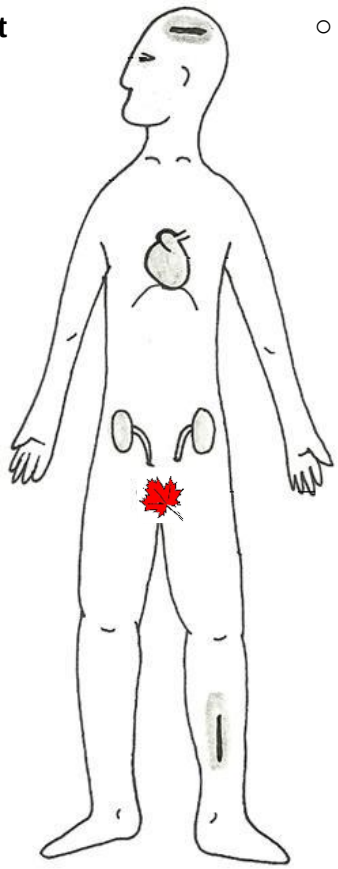
- Septicemia
- Hematological disorder
- Hemorrhagic exanthemas
- Remittent
  - Temperature raised throughout the day
  - Difference between maximum and minimum temp' is > 2 °F
- Intermittent
  - High peaks with return to normal at some point each day
  - Suggests abscess, septicemia, malaria
- Continuous
  - Temperature raised throughout the day
  - Difference between maximum and minimum temperature is < 2 °F
  - Suggests
    - SBE
    - Viral pneumonia
    - Miliary TB
    - Typhoid fever
- Relapsing (undulating)
  - Periods of normal temperature between periods of high temperature
  - Suggestive of
    - Brucellosis
    - Spirochaetal infection
    - Reticulosis
    - Bite and scratch fevers

➢ Organs

o CNS	- Delirium
o Lung	- Acute respiratory stress syndrome (ARDS) - Pneumothorax (from mechanical ventilation) - Aspiration pneumonitis or pneumonia - Pleural effusions - Nosocomial pneumonia - Pulmonary embolism (PE)
o Heart	- Pericardial effusions
o Kidney	- Acute renal failure - pH, fluid and electrolyte disturbances

- Blood
  - Disseminated intravascular coagulation (DIC)
  - Thrombocytopenia
  - Deep vein thrombosis (DVT), +/- PE
- GI tract
  - Malnutrition
  - Stress ulceration
  - Gastroparesis
  - Hepatic dysfunction
  - ↑ risk of drug adverse effects (AEs), from ↓ hepatic metabolism of certain drugs

The Septic Patient



- Skin
  - IV line site infections
  - Needle tracks
  - Leg ulcers or pressure sores
  - Boils or cellulitis
  - Petechial rash (meningococcal disease)
- Legs
  - Poor peripheral perfusion
- CNS
  - Meningitis
  - Cerebral abscess
  - Change in level of consciousness
  - Focal neurological signs
  - Fungal emboli in retina (disseminated candidemia)
- Heart
  - Hypotension
  - Endocarditis
  - New murmurs
  - Embolic lesions
- Rectum
  - Abscess
  - Enterobacteraciae
- GU
  - Toxic shock syndrome

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 296.

➢ Classification of Sepsis, Severe Sepsis and Septic Shock

Clinical Staging	Diagnostic Criteria
○ Sepsis	- Clinical evidences suggestive of infection with: - Signs of a systemic inflammatory response to infection (≥ 2 of the following): - Tachypnea (> 20 breaths/minute or $PaCO_2$ < 32 mm Hg [< 4.3 kPa]) - Tachycardia (> 90 beats/minute) - Hyperthemia (> 38 °C) - WBC > 12 x 10^9 cells/L, or < 4 x 10^9 cells/L, or > 10% immature (band) forms
○ Severe sepsis	- Sepsis with hypotension (systolic blood pressure < 90 mm Hg or a 40 mm Hg decrease from baseline in the absence of other causes) - Organ dysfunction and perfusion abnormalities such as: - Oliguria: < 0.5 mL/kg for at least 1 hour in patients with urinary catheters - ↑ plasma lactate (> normal upper limit) - Altered mental status
○ Septic shock	- Severe sepsis as defined above, despite adequate fluid resuscitation

Note: Patients who are on pressor agents may not be hypotensive

Reproduced with permission: Therapeutics Choices. Sixth Edition. Ottawa, *Canada: Canadian Pharmacist Association* 2012, Table 1, page 1490.

➢ Laboratory

- In the setting of sepsis, give 3 clinical and laboratory changes suggestive of hypotension and hypoperfusion.
  - Lactic acidosis
  - Acute ↓ loss of consciousness (LOC) or change in mental function
  - Acute kidney injury (AKI)

- Give the treatment for **septic shock**.

  Treat the underlying cause(s)

  - Heart
    - Central venous pressure (CVP), 8 – 12 mm Hg
      - IV fluids to correct CVP
      - May require 10 – 20 L/day
    - Mean arterial pressure (MAP) > 65 mm Hg
      - Vasoactive agents (Norepinephrine or dopamine (vasopressin) to correct MAP (if correction of CVP not sufficient)
      - MAP = (SBP + 1DBP) / 3
  - Lung
    - Supplemental O_2
    - Mechanical ventilation
    - Packed RBC for S cvo_2 < 70%, to maintain hematocrit > 30%
    - Inotropic agents if S cvo_2< 70% despite RBC transfusion
    - Sv CO_2
      - Hematocrit (Hct)
        - < 30% - transfusion
        - ≥ 30% - dopamine or dobutamine (inotropes)

        ] to correct $SvCO_2$ once CAP and MAP corrected
    - Acute respiratory distress syndrome (ARDS)
      - Mechanical ventilation 6 mL/kg and plateau pressures
  - Endocrine
    - Blood sugar
    - Corticosteroids
      - Low dose if systolic pressure < 90 mm Hg despite IV fluids or vasopressors
        - Do not use high-dose, or for toxic shock syndrome
  - Renal
    - Maintain UO (urine output) > 0.5 mL/kg per hour
    - Use above measures of fluids, vasopressors, steroids

Pearl and Gem

- For septic shock, use low–dose, not high–dose corticosteroids
- For toxic shock syndrome, do **not** use corticosteroids

- Ceftaroline
  - Community–acquired non–MRSA pneumonia
- Daptomycin
  - *S. aureus* bacteremia when there is resistance to
  - Severe skin infections; vancomycin, i.e. minimal inhibitory concentration (MIC) > 2 mcg/mL
- Doripenem
  - Complicated
    - UTI and pyelonephritis
    - Intraabdominal infections
- Linezolid
  - Vancomycin–resistant enterococcus faecium infections
  - Nosocomial skin infections
  - Community–acquired pneumonia (CAP)
- Telavancin
  - Complicated skin infections
- Tigecycline
  - Complicated
    - Skin infection
    - Intraabdominal infection
  - CAP

- Give the empiric antibiotics for sepsis, and the early use of appropriate antibiotics as combined therapy.
  - Community–acquired infection
    - Cephalosporin or carbapenem ± vancomycin
  - Healthcare–associated infection
    - Especially patients who had received
      - Antibiotics
      - Immunosuppressants
      - Chemotherapy
    - Vancomycin plus
    - β–lactam (anti–pseudomonas), plus
    - Fluoroquinolone or aminoglycoside

Abbreviations: DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure

- Why elder individuals may have urinary incontinence ("**DRIP**")?
  - **D**elirium or diabetes mellitus
  - **R**estricted mobility and retention
  - **I**nfections (UTI) or impaction of stool
  - **P**sychological and pills (long acting sedatives, diuretics, anticholinergic agents)

Source: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, page 30.

Clinical Gems

- About 1/3 of patients treated for smoke inhalation from fires has associated **cyanide toxicity**.
- **Angioedema** may occur:
  - - As a part of anaphylaxis resulting from activation of IgE on the surface of mast cells and basophils
  - - Not as a part of anaphylaxis (not mediated by IgE release), such as from:
    - Brucellosis
    - Trauma
    - Infection
    - Drugs (i.e. ACE inhibitors)
    - C1 esterase (inhibitor) deficiency
    - Possibly associated with lymphoproliferative disorder

FLUSHING

- Perform a directed physical examination for flushing.
  - Anxiety
  - Skin disease
    - Acne
    - Rosacea
    - Photosensitive dermatitis
  - Drugs
    - Alcohol
    - Ca^{2+} channel blockers
  - Food
    - Scombroid poisoning

- Tumor
  - Carcinoid tumors
    - Medullary thyroid cancer
    - Systemic mastocytosis

Note: Skin conditions or self–limiting infections cause sweating without flushing

Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 54.

CLASS A BIOTERRORISM AGENTS

To be covered here:

- Anthrax
- Smallpox
- Plague
- Botulism
- Tularemia
- Viral hemorrhagic fever

Anthrax

- Definition
  - "Anthrax infection is caused by the bacterium *Bacillus anthracis*……to describe the destructive black eschar associated with cutaneous disease. This gram–positive, "box cow"–shaped, aerobic, non–motile bacillus is found in soil worldwide, predominantly in agricultural areas". (MKSAP 16, Infectious disease 2012, page 57)
  - Spores are inhaled, ingested, or contact the skin

- Clinical
  - Pulmonary anthrax
    - May become fulminant and cause death
    - Diagnosis
      - Culture } sputum, blood tissue
      - PCR }
      - Chest X–ray showing wide mediastinum (hemorrhagic lymphadenopathy)
    - Treatment
      - For 60 days, IV for 2 weeks, then *po* for 7 weeks
      - Ciprofloxacin, or
      - Doxycycline plus 1 or 2 of the following:
        - Penicillin
        - Ampicillin

- Cutaneous anthax
  - Must be treated, otherwise mortality rate is ~ 15% due to secondary bacteremic spread
- GI anthax
  - Must also be treated because of mortality rate of ~ 40%

Please see standard textbook or recent reviews such as UptoDate or MKSAP 16, Infectious disease 2012, Table 30, page 56.

- Prophylaxis
  - Antibiotics
    - Ciprofloxacin, or
    - Doxycycline
  - Anthrax vaccine

Small pox (Variola)

- Clinical
  - Sites in human body parts, infects mucosa of mouth and pharynx
    - Face
    - Arms
    - Hands
    - Legs
    - Feet
  - Synchronous (for any part of the body, i.e. face, skin lesions are all at the same stage of maturity)
  - Macules → papules → vesicles → pustules → scabs or crusts
  - Contagious until scabs or crusts have cleared
  - Affects the eyes → keratitis → ulcers of cornea → blindness
  - Mortality rate ~ 30% (variola minor, MR < 1%)

- Give the clinical features which help to distinguish the rash of chicken pox (varicella) from smallpox (variola).

Disease	Initial site	Spreads (distribution)	Stage of maturation at one site
○ Chickenpox	- Trunk	▪ Periphery (centripedal)	- Asynchronous
○ Smallpox	- Buccal mucosa, pharynx	▪ Face, arms / legs, hand / feet (centrifacial)	- Synchronous

- Diagnosis
  - PCR assays
  - Contact CDC (Centres for Disease Control and Prevention) http://emergency.cdc.gov/agent/smallpox/diagnosis/#diagnosis
- Treatment
  - Cidofovir
  - Vaccination
    - Active post–exposure administration to patient
    - Close contacts ("ring vaccination")

Plague

- Causes and associations
  - *Yersinia pestis*
  - Gram–negative coccobacillus (bipolar staining, shape of a safety pin)
  - Infects rats and cats → flea bite in humans
- Clinical
  - Purulent lymphadenitis near site of flea bite
  - Pneumonic
    - Primary
    - Secondary, from
      - Prurulent nodes
      - Septicemia
  - Septicemia
- Diagnosis
  - Gram stain
    - Blood
    - Sputum
- Treatment
  - Symptomatic
    - Antibiotics
      - Streptomycin or gentamycin, or
      - Fluoroquinolone, or
      - Doxycycline for 10 days
    - Isolation respiratory droplet precautions for 2 days after start of antibiotics
  - Asymptomatic contacts
    - Prophylactic fluoroquinolone or doxycycline for 7 days
  - Vaccination
    - Not available
- Prognosis
  - Mortality rate without treatment ~ 100%

Botulism

- Causes and associations
  - *Clostridium botulinum*, anaerobic gram–positive spore–forming bacillus
  - Release of highly lethal toxin (blocks acetylcholine–mediated neurotransmission)
  - Inhalation, ingestion, skin contact
- Clinical
  - "4 Ds"
    - Descending flaccid paralyses (diaphragm involvement → respiratory failure)
    - No fever
    - Mental changes
- Diagnosis
  - Identify toxins (skin, stool, vomitus, contaminating food)
- Treatment
  - Rapid use of antitoxin (trivalent, derived from horses)
  - Limitation: does not reverse toxin–inhibited neurotransmission of Ach

Tularemia

- Causes and associations
  - Gram–negative coccobacilllus, *Francisella tularensis,* the organism affects arthropod (ticks) which bites human
  - Also transmitted by inhalation or ingestion
- Clinical
  - Pneumonia → respiration or ingestion
  - Typhoid–like illness
  - Septicemia → septic shock
  - Mortality rate ~ 30%

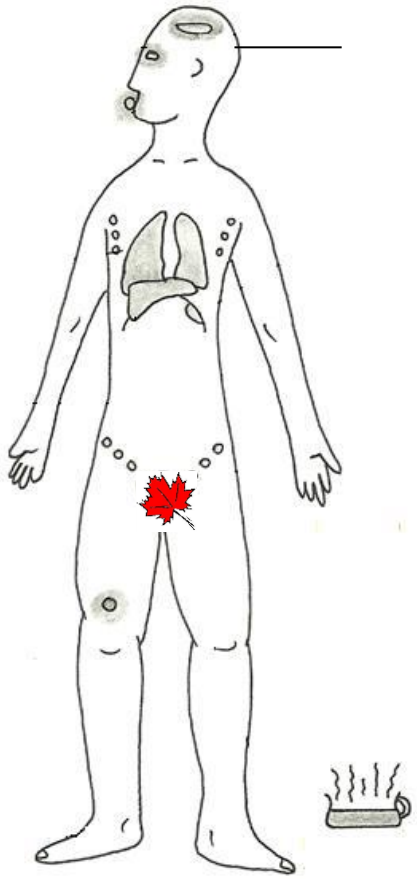
- Diagnosis
  - Serology
  - Culture (too slow)
  - Tissue
    - Immunofluorescence
    - PCR
    - Granulomatous infiltration
    - Infiltration
      - Lobar
      - Subsegmental
      - Oval
    - Pleural effusions
    - Hilar lymphadenopathy
  - Chest X–ray
- Treatment
  - Streptomycin, or
  - Gentamycin for 7 to 14 days
  - Post–exposure prophylaxis
    - Ciprofloxacin, or
    - Doxycycline
  - Vaccination: not available

"Mediocrity is metric modulation, bringing people back (regression) to the mean."

Grandad

TRAVEL MEDICINE

- Give the causes of **fever in the returned traveler**.



Jaundice
Hepatitis
Malaria
Leptospirosis
Yellow fever

Vomiting
GI pathogens
Malaria

Hepatomegaly
Amebic liver abscess
(often tender)
Hepatitis
Typhoid
Malaria
Leptospirosis

Skin lesions

itive
irment/delirium
ia
nant hepatic failure
encephalitis

Spenomegaly
Malaria
Typhoid
Brucellosis
Visceral leishmaniasis
Rickettsial diseases

Lymphadenopathy
common in many
nfections)
Rickettsial infections
HIV
Plague (localized, tender)
Brucellosis
Filariasis
Visceral leishmaniasis

Diarrhea
GI pathogens

○ Rose spots	-	Typhoid
○ Eschar	-	Tick and scrub typhus
	-	Anthrax
○ Petechiae/ hemorrhage	-	Viral hemorrhagic fevers
	-	Leptospirosis
○ Maculopapular	-	Dengue, tick typhus, syphilis, arboviral infections, leptospirosis, HIV
○ Chancre	-	African trypanosomiasis

Adapted from: Davey, P. *Wiley-Blackwell*, 2006 page 76.

- Causes and associations
  - Bacteria
    - Typhoid fever
      - *Salmonella enterica* serotype Typhi (*S. typhi*)
    - Travellers' diarrhea
      - Multiple organisms
    - Brucellosis
      - Brucella
  - Viruses
    - Dengue fever
      - Flaviviridae (DENV–1 to DENV–4)
    - Mononucleosis syndrome
      - Cytomegalovirus (CMV)
      - Epstein-Barr virus (EBV)
    - Hepatitis A virus
  - Parasites
    - Malaria
      - Plasmodium species
  - Rickettsia
    - *Rickettsia typhi*
    - *R. prowazekii*
  - Fungi
    - *Histoplasma capsulatum*
    - Coccidioides spaces
    - *Penicillium marneffei*
    - More common in HIV infected and immunocompromised persons,
    - *P. marneffei* contracted in SE Asia and China

Brucellosis

- Causes and associations
  - Gram–negative coccobacillus *Brucella* species
  - Inhalation
  - Ingestion
    - Unpasturized milk
    - Undercooked meat
  - Skin direct contact

- Clinical
  - Night sweats
  - *Rickettsia*
  - Heart: endocarditis
- Diagnosis
  - Culture
    - Blood
    - Bone marrow
  - Serological tests
- Treatment
  - Doxycycline plus rifampin plus streptomycin or gentamycin

Dengue Fever

- Causes and associations
  - Viruses of the Flaviviridae (DENV–1 to –4) family are carried by mosquitos
- Clinical
  - Febrile illness
    - A second “saddleback” febile pattern may develop
  - Headache retro–orbital pain
  - Bleeding
    - Purpura
    - Conjunctival injection
  - Back pain
    - “breakbone fever” affecting lumbosarcral region
  - Rash (measles–like) as the fever subsides → petechial on back of the hands and feet (exterior surfaces)
  - Liver failure
- Diagnosis
  - Real–time reverse transcriptase polymerase chain reaction (PCR) of blood
  - Serologic testing of serum, acute and convalescent
  - ELISA test
- Treatment and vaccination
  - Supportive care only

Malaria

- Causes and associations
  - *Plasmodium* species parasites, transmitted by
    - bite of female *Anopheles* mosquito
  - Parasite enters RBCs
  - Multiple thrombosis occur in small blood vessels
  - *P. falciparum*
    - Common species
    - Severe risk of chloroquine resistance
    - Potentially lethal
- Clinical
  - CNS
    - ∆ level of consciousness (LOC)
    - Seizures
  - Liver
    - Hepatic failure
  - Kidney
    - Aacute kidney injury (AKI)
    - Metabolic acidosis
  - Endocrine
    - Hypoglycemia
  - Blood
    - Disseminated intravascular (DIC)
    - Thrombocytopenia coagulation
    - Hemolysis (intravascular)
- Diagnosis
  - Peripheral blood smear
  - PCR, and other molecular technique to determine species
- Treatment
  - Chemoprophylaxis for endemic areas
    - *Plasmodium falciparum*
      - Chloroquine–sensitive
      - Chloroquine–resistant

	P. vivax		
		Treatment stat & travel	
Drug	Dose	Start before	Stop after
○ Mefloquine	250 mg *qw*	1–2 weeks	4 weeks
○ Atovaquone / proguanil	250 mg/100 mg *od*	1–2 days	7 days
○ Doxycycline	100 mg *od*	1–2 days	4 weeks

- Note
  - Choice of chemo–prophylaxis depends upon destination
  - Pregnant women should not place themselves and thus their unborn child at risk and travel to an area here malaria is present

Please see standard textbooks for further recommendations about chemoprophylaxis fo malaria. Also see http://www.nc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-disease-related-to-travel/malaria.htm

- It is recommended that a pregnant women should **not** travel to a malaria is endemic places, so as to prevent the morbidity of this infection to the mother and child.
- However, in the event that the travel is essential, give the recommended prophylaxis.
  - Chloroquine sensitive
    - Chloroquine 500 mg OW
  - Chloroquine resistant
    - Mefloquine 250 mg OW

Abbreviation: OW, once weekly

Rickettsioses

- Causes and associations
  - Intracellular gram–negative bacteria transmitted by fleas, lice, mites, ticks; i.e.:
    - *Rickettsia typhi* fleas vector
    - *R. prowazekii* body lice
- Clinical
  - Febrile illness
  - Rash
    - Maculopapular
    - Vesicular
    - Petechial
- Diagnosis
  - Culture of involved skin
  - Biopsy immunohistochemistry
  - PCR
- Treatment
  - Doxycycline
  - No vaccine available

Typhoid Fever

- Causes and associations
  - *Salmonella enterica* serotype typhi (*Salmonella typhi*)
  - Consumption of food and water contaminated by human feces
- Clinical
  - Fever "enteric" everyday for 4 – 8 weeks
  - Diarrhea
  - Bleeding and bowel perforation (2 to 3 weeks after beginning of infection)
  - "rose spot rash" (1 to 4 weeks after beginning of infection)
  - High risk of chronic state in person with cholelithiasis
- Diagnosis
  - Culture
    - Stool
    - Urine
    - Blood
    - Bone marrow
  - Serology molecular methods have replaced traditional - Wodal test for anti–O and –H antigens
- Treatment
  - Empiric therapy of choice change because of fluoroquine resistance
  - Fluoroquine or ceftriaxone
  - Typhoid vaccine
    - ~70% protection
    - Oral liver–attenuated vaccine, or
    - M cell–free Vi capsular polysaccharide vaccine

Fungal Infections Associated with Travel

- Causes and associations
  - *Coccidioides* species
  - Histoplasma sp.
  - *Penicillium marneffei*
    - High mortality rate
    - Recurrences
    - Needs treatment for life

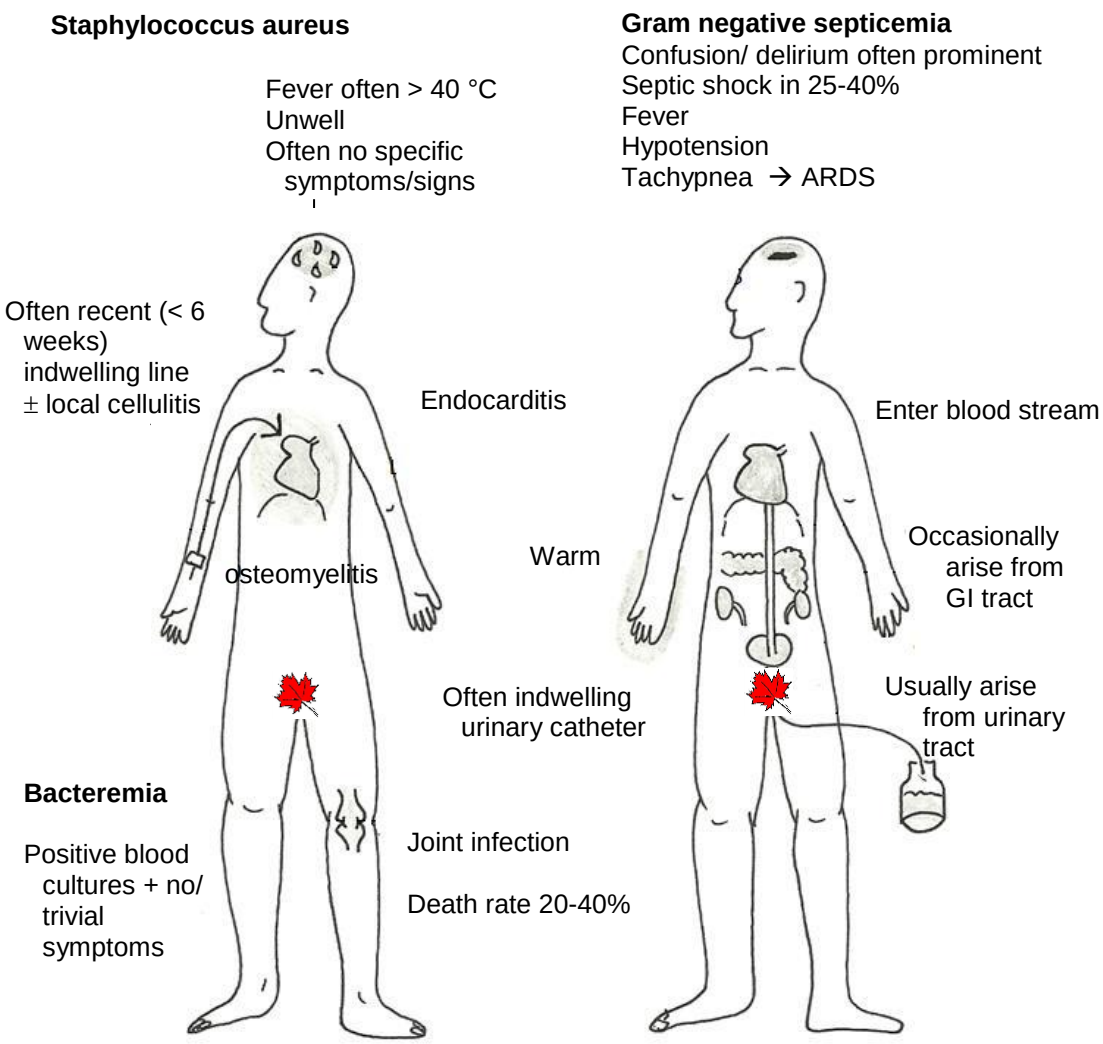
Pearl and Gem

- In *Clostridium difficile* antibiotic–associated diarrhea (CDAAD) there are presentations other than "diarrhea", including:
  - Fever
  - Rectal bleeding
  - Ileus
- CDAAD may develop in the community, and in individuals who are not previously exposed to antibiotics

HOSPITAL–ACQUIRED INFECTIONS (HAIS)

- Definition
  - Any infection which develops within 48 hours of hospitalization
  - Absence of evidence that infection was present or incubating pre–hospitalization
- Clinical

- Perform a directed physical examination for fever and infection in a patient in hospital.



Adapted from: Davey, P. *Wiley-Blackwell* 2006, page 68.

➢ Types

- Give the types of HAIs.
  - Antibiotic–associated diarrhea (AAD) including *C. difficile*
  - Catheter–associated urinary tract infection (CAUTI)
  - Central time–associated bloodstream infection (CLABSI)
  - hospital–acquired infection with multi-drug resistant organisms (HAI–MDRO)
  - Hospital–acquired pneumonia (HAP)
  - Surgical site infections (SSI)
  - Ventilator–acquired pneumonia (VAP)

Hospital–acquired pneumonia (HAP)

➢ Definitions
- HAP
  - Symptoms of pneumonia with new or progressive infiltration on chest X–ray ≥ 48 hours after hospitalization
- VAP
  - A subset of HAP, occurring > 48 hours after endotracheal intubation
- May be caused by multi–drug–resistant organisms (MDRO)
- Most cases of HAP in the ICU are VAP

➢ Risk factors

- Give the factors which ↑ risk of HAP / VAP.
  - Patient
    - Older
    - Fatal disease
    - Trauma
    - Drugs
      - Antibiotics
      - Corticosteroids
      - H2 blockers
  - CNS
    - Neurological disease
    - ↓ level of consciousness)
  - Lung
    - Ventilation
    - Underlying chronic lung disease
    - Recent large–volume aspiration

- Abdomen
  - Abdominal surgery
  - Nasogastric (NG) tube
  - Use of H2 blockers

- Give the factors which ↑ risk of MDRO.
  - Drugs
    - Antibiotics
    - Immune suppression
  - Hospital
    - ≥ 5 days hospitalization
    - Health care–associated exposures

➢ Treatment
- Depends upon risk for multi–drug–resistant organisms (MDRO)
- Risk factors for MDRO
  - Hospitalization
    - ≥ 5 days
    - From a healthcare facility
  - Drugs (recent)
    - Antibiotics
    - Immunosuppressants
- No MDRO risks
  - Ceftriaxone, or
  - Levofloxacin
- MDRO risk
  - Vancomycin, plus
  - Cefepime or ceftriaxone

- Give the rationale for the antibiotic selection for HAP/VAP associated with risk of MDRO.
  - Vancomycin – MRSA
  - Cefepime or ceftriaxone – *Pseudomonas aeruginosa*

HAI-MDRO (Hospital-acquired infections from multi-drug resistant organisms)

- Most MDROs are HAI, rather than community–acquired

➢ Causes and associations

- Give the name of the common HAI associated with MRDOs.
  - Gram–positive
    - Methicillin–resistant Staphylococcus aureus (MRSA)
    - Vancomycin–resistant enterococci (VRE)
  - Gram-negative
    - Extended–spectrum B–lactamase (ESBL)–producing Enterobacteriaceae
    - MDR strains of *P. aeruginosa*

➢ Treatment

- MRSA
  - Vancomycin
  - Linezolid
  - Clindamycin
  - Daptomycin
- VRE
  - Ampicillin
  - Linezolid
  - Daptomycin
- ESBL
  - For Carbapenem resistant
    - Carbapeman–sensitive
    - Fluoroquinolones
    - Ertapenem
    - Enterobacteriacease
    - *Pseudomonas*
    - *Acinetobacter*
    - Polymyxins
    - Tigecycline
    - Aminoglycosides

"Don't worry about the neurobiological mechanisms of motivated learning – just provide a safe, stimulating and welcoming environment."

Grandad

CAUTI (catheter–associated urinary tract infection (UTI)

- Definition
  - Symptoms or signs of UTI in patients with
  - ≥ 10^3 cfu (colony forming units)/mL
  - ≥ 1 bacterial species in urine sample

- Note: In patient with urinary catheter, pyuria does not indicate UTI.

- Clinical
  - If patient with urinary catheter has UTI symptoms, fever and cultured mental state, suspect CAUTI then culture urine and treat appropriately
  - If patient is asymptomatic, "don't go looking for trouble" do not do urine culture or urinalysis.
  - If culture is done (inappropriately) in asymptomatic patient with a urinary catheter, do not treat bacteriurea or candiduria.

- Prevention
  - Chlorhexidine skin cleaning
  - Antibiotic–coated catheters, dressings
  - Catheter–care team, i.e. TPN team

- Treatment

	Cultures		Antibiotic	Catheter
	Catheter	Blood	treatment	removal
Colonization	+	-	No	-*
Catheter–related bacteremia	+	+	1-3 wk	+/-
Complications	+	+	4-6 wk	+
	Skin site culture			
Exit–site	+	-	1 wk	+/-
Tunnel	+	-	1-3 wk	+/-

* Catheter positive, blood culture negative, or transiently positive for coagulase–negative staph' bacteremia

- Antimicrobials
  - Vancomycin, if no MRSA or no coagulase–positive *Staphylococcus*
  - Neutropenia or sepsis
  - Candidemia
    - Fluconazole
  - Candidemia plus sepsis
    - Amphotericin B or echinocandin especially when caused by Candida tropicalis, C. keusei

- Give the indications in performing transesophageal echocardiography (TEE) in patient with catheter–related infection.
  - Blood cultures positive for *S. aureus*
  - Signs of endocarditis, such as new murmur

Surgical Site Infections (SSIs)

- Give the pre– and intra–operative measures which are useful to ↓ risk of surgical site infection (SSI)

Preoperative	Hair	Clean but do not shave
	Skin	Chlorhexidine cleaning solution
	Lungs	Supplement O_2
	Operating room	Only necessary or staff Checklist use for compliance to quality improvement procedures
Intraoperative-antibiotics	Antibiotics	Vancomycin and fluoquinolone Start 1 – 2 hours before surgical incision Repeat as needed during long procedure Stop antibiotics within 24 hours

CARE FOR THE ELDERLY

- Take a directed history for functional assessment in the elderly.
  - Activities of daily living (ADL)
    - Transfers out of bed
    - Going to the toilet
    - Eating
    - Dressing
    - Getting around the home
    - Bathing
    - Food preparation
    - Stairs
    - Walking

Reasons for Falls in Seniors

- Physiologic
  - ↓ visual acuity
  - ↓ night vision
  - ↓ sensory awareness, touch
  - ↑ body sway, ↓ righting mechanisms
- Pathologic
  - Cardiac
    - Myocardial infarction
    - Orthostatic hypotension
  - Neurological
    - Stroke
    - TIA
    - Dementia
    - Parkinson's disease
  - Metabolic
    - Hypoglycemia
    - Anemia
    - Dehydration
  - MSK
    - Arthritis
    - Muscle weakness
  - Drug induced
    - Diuretics
    - Antihypertensives
    - Sedatives
    - Analgesics

Abbreviations: MSK, musculoskeletal; TIA, transient ischemic attack

Adapted from: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, page 35.

Grief and Abuse

- Give the classic stages of grief.
  - Patient attempts to limit awareness of condition (shock, denial, and isolation)
  - Patient has awareness and emotional release
  - Patient experiences depression
    - Accepts the reality of loss
    - Work through the pain of grief
  - Patient has acceptance and resolution
    - Adjust to life without the deceased

Feelings that many grieving people experience.

- Anger
- Hopelessness
- Guilt
- Worthlessness

Source: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, pages 196, 198 and 199.

WOMEN'S HEALTH

Breast Cancer

- Treatment
  - Surgery
    - Lumpectomy plus radiation
      - Tumor < 5 cm
      - Localized in situ duct carcinoma
    - Mastectomy
      - Tumor > 5 cm
      - Previous radiation therapy
    - Dissection of axillary nodes
      - Only if sentinel node is positive
    - Mastectomy plus radiation
      - Close surgical margin
      - Involvement of skin
      - ≥ 4 axillary nodes

- Pharmaceuticals, after lumpectomy plus radiation

- ER / PR – positive tumor	▪ Premenopausal - Tamoxifen ▪ Postmenopausal - Aromatase–inhibitors Letrozole Anastrozole **Emaestane** ▪ Bone metastasis, or small, asymptomatic visceral metastases - Serial tamoxifen; aromatase–inhibitors - Fulvestrant, and - Megestrol acetate
- ER / PR–negative tumors, or endocrine resistant	▪ Sequential single agent chemotherapy, or ▪ Combination chemotherapy
- HER2–positve tumor	▪ Trastuzumab ± chemotherapy adjuvant therapy
- Adjuvant chemotherapy	▪ Tumor > 1 cm ▪ Any lymph node involvement
- Lytic bone disease	▪ Bisphosphonates ▪ Denosumab ▪ Radiation

- Why women with HER–2 positive breast cancer are given adjunctive therapy with trastuzumab without anthracycline agents?
  - These agents are cardiotoxic and may impair left ventricular (LV) function and lead to heart failure (HF)
  - Assessment of cardiac LV function is recommended **before** trastuzumab adjuvant therapy for HER2–positve breast cancer

- Prevention
  - If the Gail model predicts that a 35 to 60 year old woman's 5 yr risk of breast cancer is ≥ 1.66%, then tamoxifen or raloxifene may be offered, taking into account the recipient's ↑ risk of
    - Thromboembolic disease (TED)
    - Endometrial cancer
  - Tamoxifen and raloxifene reduce the risk of a woman developing breast cancer, but in some women the risk of her developing breast cancer is so high that prophylactic bilateral mastectomy and oophorectomy may be recommended.

- Give the factors which should lead to a discussion about prophylactic bilateral mastectomy and oophorectomy

o Mutation	- BRCA1 or BRCA2 gene - p53 gene
o Family history	- 1st degree relative - 2nd degree relatives of breast or ovarian cancer on the same side of the family

Disappointing

- Unlike cervical cancer, screening for endometrial cancer does not ↓ mortality
- It is not yet established that screening for ovarian cancer ↓ mortality

Cervical Cancer

Stage	
o IA1	
- Child–bearing desired	▪ Loop electrosurgical excision ▪ Cervical conisation
- Child–bearing not desired	▪ Hysterectomy
o II, III, IV	- Radiation - Chemotherapy, cisplatin
o Metastatic disease	- Local radiation - Chemotherapy

MEN'S HEATH

Prostate Cancer

A man presents with acute urinary retention, and a prostate cancer is suspected. The prostate specific antigen (PSA) concentration is increased.

- Give the next step for the assessment.
  - Relieve the obstruction and repeat the PSA
  - Any cause of urinary retention will increase the PSA concentration.

- Treatment options
  - Radical prostatectomy
  - Radiation
  - Radiation plus androgen deprivation therapy with gonadotropin–releasing hormone agonist (hormonal therapy)
  - Hormonal therapy
  - Docetaxel

SEXUAL ABUSE ACCOMMODATION SYNDROME

- Experienced by people who have suffered sexual abuse as children may experience
  - Secrecy and silence
  - Helplessness and vulnerability
  - Entrapment and accommodation
  - Delayed, conflicted, and unconvincing disclosure
  - Retraction

Source: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, pages 86 to 88.

For an excellent background of:

- A directed history for physical abuse, please see: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, pages 73 and 74.
- A directed history for sexual abuse, please see: Jugovic, P.J., *et al*. *Saunders/Elsevier*, 2004, pages 86 and 87.
- Reasons why the abused often fail to speak out about their mistreatment and kinds of elder abuse, please see: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, page 209.

SO YOU WANT TO BE A GOOD GENERAL PHYSICIAN!

- You say that the patient "**looks his/her stated** age. Give the conditions make you look older or younger than you actually are?

    - Looks older
        - Smoking
        - Drinking in excess
        - Sunlight in excess
        - Chronic illness or cancer
        - Progeria (pathological acceleration of aging)
    - Looks younger
        - Hypogonadism
        - Panhypopituitarism
        - You wish!

Adapted from: Mangione, S. *Hanley & Belfus* 2000, page 11.

For an excellent background of how to:

- Take a directed history for HIV disease in a man having sex with men (MSM), see: Jugovic, P.J., *et al*. *Saunders/Elsevier*, 2004, pages 45 and 46.

- Take a focused history for Gay and Lesbian health issues, see: Jugovic, P.J., *et al*. *Saunders/Elsevier*2004, pages 40 and 41.

JUST A FEW OF THE DRUGS TO AVOID IN PREGNANCY-TERATOGENIC

- Certain
    - Coumadin
    - Methotrexate
    - Misoprostol
    - Thalidomide
- Possible
    - Diazepam
    - Fluconazole
    - Statins

Diav-Citrin O and Koren G. Appendix II. In: Therapeutic Choices. Grey, J., Ed. 6th Edition, *Canadian Pharmacists Association*: Otttawa, 2011, page 1722-4.

Warning

Use of alcohol in any amounts is **not** compatible with pregnancy or breastfeeding.

TOXIC SYNDROMES FROM DRUG OVERDOSE

- Perform a focused physical examination to determine the cause of drug toxicity.

	Sym	Chol	Anti-Chol	Opioids
○ Eyes	Mydriasis	Myosis	Mydriasis	Miosis
○ CNS activity	↑	↓	↑	↑
○ Secretions				
- Tears	↓	↑	↓	
- Salivation	↓	↑	↓	
- Bronchorrhea	↓	↑	↓	
- Sweating	↑	↓	↑	
○ Heart				
- HR	↑	↓	↑	↓
- ↑ BP	↑		↑	↓
- RR	↑		↑	↓
- Temp	↑		↑	
○ GU				
- Urination		↑		
○ GI				
- Defection		↑		
- Vomiting		+		

Abbreviations: anti–chol, anti-cholinesterases; BP, blood pressure; Chol, cholinesterases; HR, heart rate; RR, respiratory rate; Sym, sympatheticomimetics; Temp, temperature

LIFESTYLE ISSUES

- Take a directed history of lifestyle issue.

  - **History of Present Illness** (HPI) **– L DOCC SPARC CIP**
    - **L**ocation
      - Where is the chief complaint experienced?
    - **D**uration
      - How long does the chief complaint last?
    - **O**nset
      - When did the chief complaint start?
    - **C**ourse
      - What are the changes in the chief complaint over time?
    - **C**haracter
      - Describe the quantity and quality of the chief complaint
    - **S**everity
      - Grade the chief complaint on a scale from 0 (no pain) to 10 (worst pain the patient can image) both for its time of onset and the present
    - **P**alliating or provoking factors
      - What makes the chief complaint better and worse?
    - **A**ssociated S&S
      - What are the signs and symptoms presenting as a complex with the chief complaint?
    - **R**isk factors
      - What are the factors known to enhance chances of having the chief complaint?
    - **C**onstitutional signs
      - Fever, chills, night sweats, changes in sleep, energy level, weight, and appetite
    - **C**ausation
      - What does the patient think the cause is?
    - **I**mpact on the patient
      - How has the illness affected the patient?
    - **P**atient's action
      - What has the patient done for the complaint (s)?

- **Past Medical History** (PMH) **- SHIAMS**
  - **S**urgeries
    - Type, when, outcome (s)
  - **H**ospitalizations
    - Condition, when hospitalized, outcome (s)
  - **I**llnesses
    - In adults, always ask about HTN, DM, Hx of cancer, as well as duration and treatments
  - **A**llergies
    - Drugs, descriptions of reaction (s), MedAlert? EpiPen?
  - **M**edications
    - Types and dosing
  - **"S**ins"
    - Smoking or Alcohol or drug abuse
- Family history
- Causes and associations
- Complications

Abbreviations: HPI, history of present illness; PMH, past medical history

Source: Jugovic, P.J., *et al*. *Saunders/Elsevier* 2004, pages 5 to 9.

"We need to move forward our decisions:
we must operationalize."

Grandad

ONLINE RESOURCES:

MedEdPORTAL: https://www.mededportal.org/

Portal of online geriatric education: http://www.pogoe.org/

AGA educator resources: http://www.gastro.org/gi-fellowship/educator-resources

http://www.gastro.org/practive/medical-osition-statements

Home parenteral Nutrition: www.oley.org

Intestinal transplantation: http://www.intestinaltransplant.org

CCFA: http://www.ccfa.org

CCFC (Crohn's and Colitis Foundation of Canada): www.ccfc.ca

http://www.pathology.pitt.edu/lectures/gi

www.orl.cz/ehorroby/ustni/vestibulum/veozena

http://www.pathologyatlas.com

http://www.mayoclinic.org/gi-risk/mayomodel2.html

http://mayoclini.org/meld/mayomodel6.html

www.gastro.org/practice/meicacl-osition-statements

Natural Comprehensive Cancer Network (NCCN) guidelines: www.nccn.org

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/201917lbl.pdf

http://www.aidsinfo.nih.gov/guidelines/

http://www.fda.gov/Drugs/DrugSafety/ucm291119.htm

http://www.fda.gov/Drugs/DrugSafety/ucm291119.htm

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm256299.htm

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm291144.htm

http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm211796.htm

www.aasid.org/practiceguidelines/Page/default.aspx

http://www.accessdata.fda.gov/drugsatfda_does/label/2011/201917lbl.pdf

www.aasld.org/practiceguidelines/Page/default.aspx

National Endoscopy Program : www.grs.nhs.uk

*MELD, Model for End–Stage Liver Disease, available online calculator: www.mayoclinic.org/meld/mayomodel7.html

www.motherisk.org/women/index.jsp

National Endoscopy Program : www.grs.nhs.uk

CAPstone: http://www.giandhepatology.com

MedicineNet: www.medicinenet.com/irritable_bowel_syndrome/article.htm

IBS Support group: www.ibsgroup.org

UpdateToDate: www.uptodate.com/patients/index

International Association for the Study of Obesity: http://www.iaso.org

Liver and intrahepatic bile ducts. www.PathologyOutlines.com

Medical council of Canada. Weight Gain/Obesity. http://mcc.ca/Objectives_Online/

Medical Council of Canada. Weight Loss/ Eating Disorders/ Anorexia http://mcc.ca/Objectives_Online/

Medical council of Canada. Weight loss/Eating Disorders/Anorexia. http://mcc.ca/Objectives_Online/

http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm213038.htm.

Me'decins San Frontieres: http://www.msf.org

Recommendations about chemoprophylaxis for malaria. Also see http://www.nc.cdc.gov/travel/yellowbook/2012/chapter-3-infectious-disease-related-to-travel/malaria.htm

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